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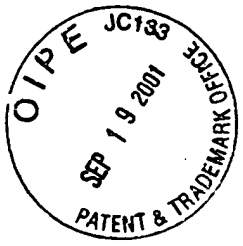

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PATENT APPLICATION

STREPTOCOCCUS SUIS VACCINES AND DIAGNOSTIC TESTS

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STREPTOCOCCUS SUIS VACCINES AND DIAGNOSTIC TESTS

[0001] **Cross-reference to Related Applications.** This application claims priority to, and is a continuation of, International Application No. PCT/NL99/00460, filed on July 19,1999, designating the United States of America, the contents of which are incorporated herein by this reference, the PCT International Patent Application itself claiming priority from European Patent Office Application Serial No. 98202465.5 filed July 22, 1998 and European Patent Office Application Serial No. 98202467.1 filed July 22, 1998.

[0002] **Technical Field.** The invention relates to *Streptococcus* infections in pigs, vaccines directed against those infections, tests for diagnosing *Streptococcus* infections and bacterial vaccines. More particularly, the invention relates to vaccines directed against *Streptococcus* infections.

Background of the Invention

[0003] *Streptococcus species*, of which a large variety cause infections in domestic animals and man, are often grouped according to Lancefield's groups. Typing according to Lancefield occurs on the basis of serological determinants or antigens that are, among others, present in the capsule of the bacterium, and allows for only an approximate determination. Often, bacteria from different groups show cross-reactivity with each other, while other Streptococci [can not]cannot be assigned a group-determinant at all. Within groups, further differentiation is often possible on the basis of serotyping. These serotypes further contribute to the large antigenic variability of Streptococci, a fact that creates an array of difficulties within diagnosis of and vaccination against Streptococcal infections.

[0004] Lancefield group A *Streptococcus species* (Group A streptococci "GAS", *Streptococcus pyogenes)* are common in children, causing nasopharyngeal infections and complications thereof. Among animals, cattle are especially susceptible to GAS, and the resulting mastitis.

[0005] Group A streptococci are the etiologic agents of streptococcal pharyngitis and impetigo, two of the most common bacterial infections in children, as well as a variety of less common, but potentially life-threatening, infections including soft tissue infections, bacteremia, and pneumonia. In addition, GAS are uniquely associated with the post-infectious autoimmune syndromes of acute rheumatic fever and post streptococcal glomerulonephritis.

[0006] Several recent reports suggest that the incidence of both serious infections due to GAS and acute rheumatic fever has increased during the past decade, focusing renewed interest on defining the attributes or virulence factors of the organism that may play a role in the pathogenesis of these diseases.

[0007] GAS produce several surface components and extracellular products that may be important in virulence. The major surface protein, M protein, has been studied in the most detail and has been convincingly shown to play a role in both virulence and immunity. Isolates rich in M protein are able to grow in human blood, a property thought to reflect the capacity of M protein to interfere with phagocytosis, and these isolates tend to be virulent in experimental animals.

[0008] Lancefield group B *Streptococcus* ("GBS") are most often seen in cattle, causing mastitis[,]; however, human infants are susceptible as well, often with fatal consequences. Group B streptococci (GBS) constitute a major cause of bacterial sepsis and meningitis among human neonates born in the United States and Western Europe and are emerging as significant neonatal pathogens in developing countries as well.

[0009] It is estimated that GBS strains are responsible for 10,000 to 15,000 cases of invasive infection in neonates in the United States alone. Despite advances in early diagnosis and treatment, neonatal sepsis due to GBS continues to carry a mortality rate of 15 to 20%. In addition, survivors of GBS meningitis have 30 to 50% incidence of long-term neurologic sequelae. Over the past two decades, increasing recognition of GBS as an important pathogen for human infants has generated renewed interest in defining the bacterial and host factors important in virulence of GBS and in the immune response to GBS infection.

[0010] Particular attention has focused on the capsular polysaccharide as the predominant surface antigen of the organisms. In a modification of the system originally developed by Rebecca Lancefield, GBS strains are serotyped on the basis of antigenic differences

in their capsular polysaccharides and the presence or absence of serologically defined C proteins. While GBS isolated from non[-]human sources often lack a serologically detectable capsule, a large majority of strains associated with neonatal infection belong to one of four major capsular serotypes, la, lb, II or III. The capsular polysaccharide forms the outermost layer around the exterior of the bacterial cell, superficial to the cell wall. The capsule is distinct from the cell wall-associated group B carbohydrate. It has been suggested that the presence of sialic acid, in the capsule of bacteria that causes meningitis, is important for allowing these bacteria to breach the blood-brain barrier. Indeed, in *S. agalactiae*, sialic acid has been shown to be critical for the virulence function of the type III capsule. The capsule of *S. suis* serotype is composed of glucose, galactose, N-acetylglucosamine, rhamnose and sialic acid.

[0011] The group B polysaccharide, in contrast to the type-specific capsule, is present on all GBS strains and is the basis for serogrouping the organisms into Lancefield's group B. Early studies by Lancefield and co-workers showed that antibodies raised in rabbits against whole GBS organisms protected mice against challenge with strains of homologous capsular type, demonstrating the central role of the capsular polysaccharide as a protective antigen. Studies in the 1970s by Baker and Kasper demonstrated that cord blood of human infants with type III GBS sepsis uniformly had low or undetectable levels of antibodies directed against the type III capsule, suggesting that a deficiency of anticapsular antibody was a key factor in susceptibility of human neonates to GBS disease.

[0012] Lancefield group C infections, such as those with *S. equi, S. zooepidemicus, S. dysgalactiae,* and others, are mainly seen in horses, cattle and pigs, but can also cross the species barrier to humans. Lancefield group D *(S. bovis)* infections are found in all mammals and some birds, sometimes resulting in endocarditis or septicemia.

[0013] Lancefield groups E, G, L, P, U and V *(S. porcinus, S[,], canis, S. dysgalactiae)* are found in various hosts, causing neonatal infections, nasopharyngeal infections or mastitis.

[0014] Within Lancefield groups R, S, and T[,] (and with ungrouped types), *Streptococcus suis* is an important cause of meningitis, septicemia, arthritis and sudden death in young pigs (4, 46). Incidentally, it can also cause meningitis in man (1). *S. suis* strains are usually identified and classified by their morphological, biochemical and serological characteristics (58, 59,

46). Serological classification is based on the presence of specific antigenic polysaccharides. So far, 35 different serotypes have been described (9, 56, 14). In several European countries, *S. suis* serotype 2 is the most prevalent type isolated from diseased pigs, followed by serotypes 9 and 1. Serological typing of *S. suis* is performed using different types of agglutination tests. In these tests, isolated and biochemically characterized *S. suis* cells are agglutinated with a panel of 35 specific sera. These methods are very laborious and time-consuming.

[0015] Little is known about the pathogenesis of the disease caused by *S. suis*, let alone about its various serotypes such as type 2. Various bacterial components, such as extracellular and cell-membrane associated proteins, fimbriae, [hemaglutinins] hemagglutinins, and [hemolysis] hemolysin have been suggested as virulence factors (9, 10, 11, 15, 16, 47, 49). However, the precise role of these protein components in the pathogenesis of the disease remains unclear (37). It is well known that the polysaccharide capsule of various Streptococci and other [gram-positive] Gram-positive bacteria plays an important role in pathogenesis (3, 6, 35, 51, 52). The capsule enables these [micro-organisms] microorganisms to resist phagocytosis and is therefore regarded as an important virulence factor. Recently, a role of the capsule of *S. suis* in the pathogenesis was suggested as well (5). However, the structure, organization and function of the genes responsible for capsule polysaccharide synthesis *([cps]"cps")* in *S. suis* is unknown. Within *S. suis*, serotype[s] 1 and 2, strains can differ in virulence for pigs (41, 45, 49). Some type 1 and 2 strains are virulent, other strains are not. Because both virulent and non[-]virulent strains of serotype 1 and 2 strains are fully encapsulated, it may even be that the capsule is not a relevant factor required for virulence.

[0016] Attempts to control *S. suis* infections or disease are still hampered by the lack of knowledge about the epidemiology of the disease and the lack of effective vaccines and sensitive diagnostics. It is well known and generally accepted that the polysaccharide capsule of various Streptococci and other gram-positive bacteria plays an important role in pathogenesis. The capsule enables these [micro-organisms] microorganisms to resist phagocytosis and is therefore regarded as an important virulence factor.

[0017] Compared to encapsulated *S. suis* strains, non-encapsulated *S. suis* strains are phagocytosed by murine polymorphonuclear leucocytes to a greater degree. Moreover, an

increase in thickness of capsule was noted for *in vivo* grown virulent strains while no increase was observed for avirulent strains. Therefore, these data again demonstrate the role of the capsule in the pathogenesis for *S. suis* as well.

[0018] Ungrouped *Streptoccus species,* such as *S. mutans,* causing car[r]ies in humans, *S[,]* causing mastitis in cattle, and *S. pneumonia,* causing major infections in humans, and *Enterococcus faecilalis* and *E. faecium,* further contribute to the large group of Streptococci.

[0019] *Streptococcus pneumoniae* (the pneumococcus) is a human pathogen causing invasive diseases, such as pneumonia, bacteremia, and meningitis. Despite the availability of antibiotics, pneumococcal infections remain common and can still be fatal, especially in high-risk groups, such as young children and elderly people. Particularly in developing countries, many children under the age of five years die each year from pneumococcal pneumonia. *S. pneumoniae* is also the leading cause of otitis media and sinusitis. These infections are less serious, but nevertheless incur substantial medical costs, especially when leading to complications, such as permanent deafness. The normal ecological niche of the pneumococcus is the nasopharynx of man. The entire human population is colonized by the pneumococcus at one time or another, and at a given time, up to 60% of individuals may be carriers. Nasopharyngeal carriage of pneumococci by man is often accompanied by the development of protection against infection by the same serotype. Most infections do not occur after prolonged carriage but follow exposure to recently acquired strains. Many bacteria contain surface polysaccharides that act as a protective layer against the environment. Surface polysaccharides of pathogenic bacteria usually make the bacteria resistant to the defense mechanisms of the host, for example, the lytic action of serum or phagocytosis. In this respect, the serotype-specific capsular polysaccharide ("CP") of *Streptococcus pneumoniae,* is an important virulence factor. Unencapsulated strains are avirulent, and antibodies directed against the CP are protective. Protection is serotype specific; each serotype has its own, specific CP structure. Ninety different capsular serotypes have been identified. Currently, CPs of 23 serotypes are included in a vaccine.

[0020] Vaccines directed against *Streptococcus* infections typically aim to utilize an immune response directed against the polysaccharide capsule of the various *Streptococcus species,* especially since the capsule is considered a primary virulence factor for these bacteria. During

infection, the capsule provides resistance against phagocytosis and thus protects the bacteria from the immune system of the host, and from elimination by macrophages and neutrophils.

[0021] The capsule particularly confers the bacterium resistance to complement-mediated opsonophagocytosis. In addition, some bacteria express capsular polysaccharides (CPs) that mimic host molecules, thereby avoiding the immune system of the host. Also, even when the bacteria have been phagocytosed, intracellular killing is hampered by the presence of a capsule.

[0022] It is generally thought that the bacterium will [get] be recognized by the immune system through the anticapsular-antibodies or serum-factors bound to its capsule, and will, through opsonization, [get] be phagocytosed and killed only when the host has antibodies or other serum factors directed against capsule antigens.

[0023] However, these antibodies are serotype-specific, and will often only confer protection against only one of the many serotypes known within a group of *Streptococci.*

[0024] For example, current commercially available *S. suis* vaccines, which are generally based on whole-cell-bacterial preparations, or on capsule-enriched fractions of *S. suis,* confer only limited protection against heterologous strains. Also, the current pneumococcal vaccine, [that]which was licensed in the United states in 1983, consists of purified CPs of 23 pneumococcal serotypes whereas at least 90 CP types exist.

[0025] The composition of this pneumococcal vaccine was based on the frequency of the occurrence of disease isolates in the US and cross-reactivity between various serotypes. Although this vaccine protects healthy adults against infections caused by serotypes included in the vaccine, it fails to raise a protective immune response in infants younger than 18 months and it is less effective in elderly people. In addition, the vaccine confers only limited protection in patients with immunodeficiencies and hematology malignancies.

[0026] Thus, improved vaccines are needed against *Streptococcus* infections. Much attention is directed toward producing CP vaccines by producing the relevant polysaccharides via chemical or recombinant means. However, chemical synthesis of polysaccharides is costly, and capsular polysaccharide synthesis by recombinant means necessitates knowledge about the relevant genes, which is not always available, and needs to be determined for every relevant serotype.

Disclosure of the Invention

[0027] The invention provides an isolated or recombinant nucleic acid encoding a capsular *(cps)* gene cluster of *Streptococcus suis.* Biosynthesis of capsule polysaccharides has generally been studied in a number of Gram-positive and Gram-negative bacteria (32). In Gram-negative bacteria, but also in a number of [g]Gram-positive bacteria, genes which are involved in the biosynthesis of polysaccharides are clustered at a single locus.

[0028] *Streptococcus suis* capsular genes, as provided by the invention, show a common genetic organization involving three distinct regions. The central region is serotype specific and encodes enzymes responsible for the synthesis and polymerization of the polysaccharides. The central region is flanked by two regions conserved in *Streptococcus suis* which encode proteins for common functions, such as transport of the polysaccharide across the cellular membrane. However, between species, only low homologies exist, hampering easy comparison and detection of seemingly similar genes. Knowing the nucleic acid encoding the flanking regions allows type-specific determination of nucleic acid of the central region of *Streptococcus suis* serotypes, as, for example, described herein.

[0029] The invention provides an isolated or recombinant nucleic acid encoding a capsular gene cluster of *Streptococcus suis* or a gene or gene fragment derived thereof. Such a nucleic acid is, for example, provided by hybridizing chromosomal DNA derived from any one of the *Streptococcus suis* serotypes to a nucleic acid encoding a gene derived from a *Streptococcus suis* serotype 1, 2 or 9 capsular gene cluster, as provided by the invention (*see* for example, Tables 4 and 5) and cloning of (type-specific) genes as, for example, described herein. At least 14 open reading frames are identified. Most of the genes belong to a single transcriptional unit, identifying a co[-]ordinate control of these genes[, they,]. The genes and the enzymes and proteins they encode, act in concert to provide the capsule with the relevant polysaccharides.

[0030] The invention provides *cps* genes and proteins encoded thereof involved in regulation (CpsA), chain length determination (CpsB, C), export (CpsC) and biosynthesis (CpsE, F, G, H, J, K). Although, at first glance, the overall organization seemed to be similar to that of the *cps* and *eps* gene[,] clusters of a number of Gram-positive bacteria (19, 32, 42), overall

homologies are low (*see*, table 3). The region involved in biosynthesis is located at the center of the gene cluster and is flanked by two regions containing genes with more common functions.

[0031] The invention provides an isolated or recombinant nucleic acid encoding a capsular gene cluster of *Streptococcus suis* serotype 2, or a gene or gene fragment derived thereof, preferably as identified in FIG. 3. Genes in this gene cluster are involved in polysaccharide biosynthesis of capsular components and antigens. For a further description of such genes see, for example, Table 2. For example, a cpsA gene is provided functionally encoding regulation of capsular polysaccharide synthesis, whereas cpsB and cpsC are functionally involved in chain[ ]-in-chain length determination. Other genes, such as cpsD, E, F, G, H, I, J, K and related genes, are involved in polysaccharide synthesis, functioning, for example, as glucosyl[-] or glycosyltransferase. The cpsF, G, H, I, J genes encode more type-specific proteins than the flanking genes which are found more-or-less conserved throughout the species and can serve as a base for selection of primers or probes in PCR-amplification or cross-[hybridisation]hybridization experiments for subsequent cloning.

[0032] The invention further provides an isolated or recombinant nucleic acid encoding a capsular gene cluster of *Streptococcus suis* serotype 1 or a gene or gene fragment derived thereof, preferably as identified in FIG. 4.

[0033] In addition, the invention provides an isolated or recombinant nucleic acid encoding a capsular gene cluster of *Streptococcus suis* serotype 9 or a gene or gene fragment derived thereof, preferably as identified in FIG. 5.

[0034] Furthermore, the invention provides, for example, a fragment of the *cps* locus or parts thereof, involved in the capsular polysaccharide biosynthesis, of *S. suis*, exemplified herein for serotypes 1, 2 or 9, and allows easy identification or detection of related fragments derived of other serotypes of *S. suis*.

[0035] The invention provides a nucleic acid probe or primer derived from a nucleic acid according to the invention allowing species or serotype specific detection of *Streptococcus suis*. Such a probe or primer (used interchangeably herein) is, for example, a DNA, RNA or PNA (peptide nucleic acid) probe hybridizing with capsular nucleic acid as provided by the invention. Species[ ]-specific detection is provided preferably by selecting a probe or primer sequence from a

species-specific region (*e.g.* flanking region) whereas serotype[ ]-specific detection is provided preferably by selecting a probe or primer sequence from a type-specific region (*e.g.* central region) of a capsular gene cluster as provided by the invention. Such a probe or primer can be used in a further unmodified form, for example, in cross-hybridization or polymerase-chain reaction (PCR) experiments as, for example, described in the experimental part herein. The invention provides the isolation and molecular characterization of additional type[ ]-specific *cps* genes of *S. suis* types 1 and 9. In addition, we describe the genetic diversity of the *cps* loci of serotypes 1, 2 and 9 among the 35 *S. suis* serotypes known. Type-specific probes are identified. Also, a type-specific PCR, for example, for serotype 9, is provided, being a rapid, reliable and sensitive assay[,] used directly on nasal or tonsillar swabs or other samples of infected or carrier animals.

[0036] The invention also provides a probe or primer according to the invention with at least one reporter molecule. Examples of reporter molecules are manifold and known in the art[,]; for example, a reporter molecule can include additional nucleic acid provided with a specific sequence (*e.g.* oligo-dT) hybridizing to a corresponding sequence [to]in which hybridization can easily be detected, for example, because it has been immobilized to a solid support.

[0037] Yet other reporter molecules include chromophores, *e.g.* fluorochromes for visual detection, for example, by light microscopy or fluorescent [in situ hybridisation] *in situ* hybridization ("FISH") techniques, or include an enzyme such as horseradish peroxidase for enzymatic detection, [*e.g.*] for example, in enzyme-linked assays ("EIA"). Yet other reporter molecules include radioactive compounds for detection in [radiation-based-assays]radiation-based assays.

[0038] In a preferred embodiment of the invention, at least one probe or primer according to the invention is provided (labeled) with a reporter molecule and a quencher molecule, together with an unlabeled probe or primer in a PCR-based test allowing rapid detection of specific hybridization.

[0039] The invention further provides a diagnostic test or test kit including a probe or primer as provided by the invention. Such a test or test kit is, for example, a cross-hybridization test or PCR-based test[,] advantageously used in rapid detection and/or serotyping of *Streptococcus suis.*

[0040] The invention further provides a protein or fragment thereof encoded by a nucleic acid according to the invention. Examples of such a protein or fragment are[, for example,] proteins described in Table 2. For example, a cpsA protein is provided that functionally encodes regulation of capsular polysaccharide synthesis, whereas cpsB and cpsC are functionally involved in chain[ ]-in[ ]-chain length determination. Other proteins or functional fragments thereof, as provided by the invention, such as cpsD, E, F, G, H, I, J, K and related proteins, are involved in polysaccharide biosynthesis, functioning, for example, as glucosyl[-] or glycosyltransferase in polysaccharide biosynthesis of *Streptococcus suis* capsular antigen.

[0041] The invention also provides a method of producing a *Streptococcus suis* capsular antigen including using a protein or functional fragment thereof as provided by the invention, and provides therewith a *Streptococcus suis* capsular antigen obtainable by such a method.

[0042] A comparison of the predicted amino acid sequences of the *cps2* genes with sequences found in the databases allowed the assignment of functions to the open reading frames. The central region contains the type[ ]-specific glycosyltransferases and the putative polysaccharide polymerase. This region is flanked by two regions encoding for proteins with common functions, such as regulation and transport of polysaccharide across the membrane. Biosynthesis of Streptococcus capsular polysaccharide antigen using a protein or functional fragment thereof is advantageously used in chemo-enzymatic synthesis and the development of vaccines which offer protection against serotype-specific Streptococcal disease, and is also advantageously used in the synthesis and development of multivalent vaccines against Streptococcal infections. Such vaccines elicit ariticapsular antibodies which confer protection.

[0043] Furthermore, the invention provides an acapsular *Streptococcus* mutant for use in a vaccine, a vaccine strain derived thereof and a vaccine derived thereof. Surprisingly, and against the grain of common doctrine, the invention provides use of a *Streptococcus* mutant deficient in capsular expression in a vaccine.

[0044] Acapsular *Streptococcus* mutants have long been known in the art and can be found in nature. Griffith (*J. Hyg.* 27:113-159, 1928) demonstrated that pneumococci could be transformed from one type to another. If he injected live rough (acapsular or unencapsulated) type 2 pneumococci into mice, the mice would survive. If, however, he injected the same dose of

live rough type 2 mixed with heat-killed smooth (encapsulated) type 1 into a mouse, the mouse would die, and, from the blood, he could isolate live smooth type 1 pneumococci. At that time, the significance of this transforming principle was not understood. However, understanding came when it was shown that DNA constituted the genetic material responsible for phenotypic changes during transformation.

[0045] *Streptococcus* mutants deficient in capsular expression are found in several forms. Some are fully deficient and have no capsule at all, others form a deficient capsule, characterized by a mutation in a capsular gene cluster. Deficiency can, for instance, include capsular formation wherein the organization of the capsular material has been rearranged, as, for example, demonstrable by electron microscopy. Yet others have a nearly fully developed capsule which is only deficient in a particular sugar component.

[0046] Now, after much advance of biotechnology and despite the fact that little is still known about the exact localization and sequence of genes involved in capsular synthesis in Streptococci, it is possible to create mutants of Streptococci, for example, by homologous recombination or transposon mutagenesis, which has, for example, been done for GAS (Wessels []et al., *PNAS* 88:8317-8321, 1991), for GBS (Wessels []et al., *PNAS* 86: 8983-8987, 1989), for *S. suis* (Smith, ID-DLO Annual report 1996, page 18-19; Charland []et al., Microbiol. 144:325-332, 1998) and *S. pneumoniae* (Kolkman []et al., J. Bact. 178:3736-3741, 1996). Such recombinant derived mutants, or isogenic mutants, can easily be compared with the wild-type strains from which they have been derived.

[0047] In a preferred embodiment, the invention provides use of a recombinant-derived *Streptococcus* mutant deficient in capsular expression in a vaccine. Recombinant techniques useful in producing such mutants are, for example, homologous recombination, transposon [mutagenises]mutagenesis, and others, wherein deletions, insertions or (point)[-mutations] mutations are introduced in the genome. Advantages of using recombinant techniques include the stability of the obtained mutants (especially with homologous recombination and double cross[-]over techniques), and the knowledge about the exact site of the deletion, mutation or insertion.

[0048] In another embodiment, the invention provides a stable mutant deficient in capsular expression obtained, for example, through homologous recombination or [cross over]crossover integration events. Examples of such a mutant can be found herein, for example, mutants lOcpsB or 10cpsEF are stable mutants as provided by the invention.

[0049] The invention also provides a *Streptococcus* vaccine strain and vaccine that has been derived from a *Streptococcus* mutant deficient in capsular expression. In general, the strain or vaccine is applicable within the whole range of Streptococcal infections, including animals or man or with zoonotic infections. It is, of course, now possible to first select a common vaccine strain and derive a *Streptococcus* mutant deficient in capsular expression thereof for the selection of a vaccine strain and use in a vaccine according to the invention.

[0050] In a preferred embodiment, the invention provides use of a *Streptococcus* mutant deficient in capsular expression in a vaccine wherein the *Streptococcus* mutant is selected from the group composed of *Streptococcus* group A, *Streptococcus* group B, *Streptococcus suis* and *Streptococcus pneumoniae*. Herewith the invention provides vaccine strains and vaccines for use with these notoriously heterologous Streptococci, of which a multitude of serotypes exist. With a vaccine, as provided by the invention, that is derived from a specific *Streptococcus* mutant that is deficient in capsular expression, the difficulties relating to lack of heterologous protection can be circumvented since these mutants do not rely on capsular antigens, per se, to induce protection.

[0051] In a preferred embodiment, the vaccine strain is selected for its ability to survive, or even replicate, in an immune-competent host or host cells and thus can persist for a certain period, varying from 1-2 days to more than one or two weeks, in a host, despite its deficient character.

[0052] Although an immunodeficient host will support replication of a wide range of bacteria that are deficient in one or more virulence factors, in general, it is considered a characteristic of pathogenicity of Streptococci that they can survive for certain periods or replicate in a normal host or host cells such as macrophages. For example, Wiliams and Blakemore (*Neuropath. Appl. Neurobiol.*: 16, 345-356, 1990; *Neuropath. Appl. Neurobiol.*: 16, 377-392, 1990; *J. Infect. Dis.*: 162, 474-481, 1990) show that both polymorphonuclear cells and

macrophage cells are capable of phagocytosing pathogenic *S. suis* in pigs lacking anti-*S. suis* antibodies[,]; only pathogenic bacteria could survive and multiply inside macrophages and the pig.

[0053] In a preferred embodiment, the invention, however, provides a deficient or avirulent mutant or vaccine strain which is capable of surviving at least 4-5 days, preferably at least 8-10 days in the host, thereby allowing the development of a solid immune response to subsequent *Streptococcus* infection.

[0054] Due to its persistent but avirulent character, a *Streptococcus* mutant or vaccine strain, as provided by the invention, is well suited to generate specific and/or long-lasting immune responses against Streptococcal antigens. Moreover, possible specific immune responses of the host directed against a capsule are relatively irrelevant because a vaccine strain, as provided by the invention, is typically not recognized by such antibodies.

[0055] In addition, the invention provides a *Streptococcus* vaccine strain according the invention, which strain includes a mutant capable of expressing a *Streptococcus* virulence factor or antigenic determinant.

[0056] In a preferred embodiment, the invention provides a *Streptococcus* vaccine strain, according to the invention, which [strain] includes a mutant capable of expressing a *Streptococcus* virulence factor wherein the virulence factor or antigenic determinant is selected from a group of cellular components, such as muramidase-released protein ([MRP]"MRP"), extracellular factor ([EF]"EF") and cell-membrane associated proteins 60kDA heat shock protein, pneumococcal surface protein A (Psp A), pneumolysin, C protein, protein M, fimbriae, h[a]emagglutinins and [haemolysin]hemolysin or components functionally related thereto.

[0057] In a preferred embodiment, the invention provides a *Streptococcus* vaccine strain [strain comprises] including a mutant capable of over-expressing [said] the virulence factor. In this way, the invention provides a vaccine strain for incorporation in a vaccine which specifically causes a host immune response directed against antigenically important determinants of virulence (listed above), thereby providing specific protection against the determinants. Over-expression can, for example, be achieved by cloning the gene involved behind a strong promoter, which is, for example, constitutionally expressed in a multicopy system, either in a [plsamid]plasmid or via intergration in a genome.

[0058] In yet another embodiment, the invention provides a *Streptococcus* vaccine strain, according to the invention, including a mutant capable of expressing a non-*Streptococcus* protein. Such a vector-*Streptococcus* vaccine strain allows, when used in a vaccine, protection against [other] pathogens other than [Streptococcus] *Streptococcus*.

[0059] Due to its persistent but avirulent character, a *Streptococcus* vaccine strain or mutant as provided by the invention is well suited to generate specific and long-lasting immune responses, not only against Streptococcal antigens, but also against other antigens [when these are] expressed by the strain. Specifically, antigens derived from another pathogen are now expressed without the detrimental effects of the antigen or pathogen which would otherwise have harmed the host.

[0060] An example of such a vector is a *Streptococcus* vaccine strain or mutant wherein the antigen is derived from a pathogen, such as *Actinobacillus pleuropneumonia, Mycoplasmatae, Bordetella, Pasteurella, E. coli, Salmonella, Campylobacter, Serpulina* and others.

[0061] The invention also provides a vaccine including a *Streptococcus* vaccine strain or mutant according to the invention and a pharmaceutically acceptable carrier or adjuvant. Carriers or adjuvants are well known in the art[,]; examples are phosphate buffered saline, physiological salt solutions, (double-) [oil-in-water-emulsions]oil-in-water emulsions, aluminumhydroxide, Specol, block- or co-polymers, and others.

[0062] A vaccine according to the invention can include a vaccine strain either in a killed or live form. For example, a killed vaccine including a strain having (over) expressed a Streptococcal or heterologous antigen or virulence factor is very well suited for eliciting an immune response. In a preferred embodiment, the invention provides a vaccine wherein the strain is live, due to its persistent but avirulent character[,]; a *Streptococcus* vaccine strain, as provided by the invention, is well suited to generate specific and long-lasting immune responses.

[0063] The invention also provides a method for controlling or eradicating a Streptococcal disease in a population comprising vaccinating subjects in the population with a vaccine according to the invention.

[0064] In a preferred embodiment, a method for controlling or eradicating a Streptococcal disease is provided including testing a sample, such as a blood sample, or nasal or

throat swab, f[a]eces, urine, or other samples such as can be sampled at or after slaughter, collected from at least one subject, such as an infant or a pig, in a population partly or wholly vaccinated with a vaccine according to the invention for the presence of encapsulated Streptococcal strains or mutants. Since a vaccine strain or mutant according to the invention is not pathogenic, and can be distinguished from wild-type strains by capsular expression, the detection of (fully) encapsulated Streptococcal strains indicates that wild-type infections are still present. Such wild-type infected subjects can then be isolated from the remainder of the population until the infection has passed. With domestic animals, such as pigs, it is even possible to remove the infected subject from the population as a whole by culling. Detection of wild-type strains can be achieved via traditional culturing techniques, or by rapid detection techniques such as PCR detection.

[0065] In yet another embodiment, the invention provides a method for controlling or eradicating a Streptococcal disease including testing a sample collected from at least one subject in a population partly or wholly vaccinated with a vaccine according to the invention for the presence of capsule-specific antibodies directed against Streptococcal strains. Capsule specific antibodies can be detected with classical techniques known in the art, such as used for Lancefield's group typing or serotyping.

[0066] A preferred embodiment for controlling or eradicating a Streptococcal disease in a population includes vaccinating subjects in the population with a vaccine according to the invention and testing a sample collected from at least one subject in the population for the presence of encapsulated Streptococcal strains and/or for the presence of capsule-specific antibodies directed against Streptococcal strains.

[0067] For example, a method is provided wherein the Streptococcal disease is caused by *Streptococcus suis.*

[0068] The invention also provides a diagnostic assay for testing a sample for use in a method according to the invention [comprising] including at least one means for the detection of encapsulated Streptococcal strains and/or for the detection of capsule-specific antibodies directed against Streptococcal strains.

[0069] The invention further provides a vaccine including an antigen according to the invention and a suitable carrier or adjuvant. The immunogenicity of a capsular antigen provided by the invention is, for example, increased by linking to a carrier (such as a carrier protein), allowing the recruitment of T-cell help in developing an immune response.

[0070] The invention further provides a recombinant micro[-]organism provided with at least a part of a capsular gene cluster derived from *Streptococcus suis*. The invention provides, for example, a lactic acid bacterium provided with at least a part of a capsular gene cluster derived from *Streptococcus suis*. Various food-grade lactic acid bacteria (*Lactococcus lactis*, *Lactobacillus casei*, *Lactobacillus plantarium* and *Streptococcus gordonii*) have been used as delivery systems for mucosal immunization. It has now been shown that oral (or mucosal) administration of recombinant *L. lactis*, *Lactobacillus*, and *Streptococcus gordonii* can elicit local IgA and/or IgG antibody responses to an expressed antigen. The use of oral routes for immunization against infective diseases is desirable because oral vaccines are easier to administer[,] and have higher compliance rates, and because mucosal surfaces are the portals of entry for many pathogenic microbial agents. It is within the skill of the artisan to provide such micro-organisms with (additional) genes.

[0071] The invention further provides a recombinant *Streptococcus suis* mutant provided with a modified capsular gene cluster. It is within the skill of the artisan to swap genes within a Species. In a preferred embodiment, an avirulent *Streptococcus suis* mutant is selected to be provided with at least a part of a modified capsular gene cluster according to the invention.

[0072] The invention further provides a vaccine including a micro[-]organism or a mutant provided by the invention. An advantage of such a vaccine over currently used vaccines is that they include accurately defined micro[-]organisms and well-[characterised]characterized antigens, allowing accurate determination of immune responses against various antigens of choice.

[0073] The invention is further explained in the experimental part of this description without limiting the invention thereto.

Description of the Figures

[0074] FIG. 1 illustrates the organization of the cps2 gene cluster of S. *suis* type 2.

(A) Genetic map of the cps2 gene cluster. The shadowed arrows represent potential ORFs. Interrupted ORFs indicate the presence of stop codons or frame-shift mutations. Gene designations are indicated below the ORFs. The closed arrows indicate the position of the potential promoter sequences. I indicates the position of the potential transcription regulator sequence. III indicates the position of the 100-bp repeated sequence.

(B) Physical map of the cps2 locus. Restriction sites are as follows: A: *AluI;* C: *ClaI;* E[,]: *EcoRI;* H[,]: *HindIII;* K[,]: *KpnI;* M[,]: *MluI*; N[,]: *NsiI*; P[.]: *PstI*; S[.]: *SnaBI*; Sa: *SacI*; X[,]: *XbaI*.

(C) The DNA fragments cloned in the various plasmids.

[0075] FIG. 2 illustrates ethidium bromide stained agarose gel showing PCR products obtained with chromosomal DNA of S. *suis* strains belonging to the serotypes 1,2, ½, 9 and 14 and *cps2J, cpsII,* and *cps9H* primer sets as described herein.

(A) *cpsII* primers; (B) *cps2J* primers and (C) *cps9H* primers.

Lanes 1-3: serotype 1 strains; lanes 4-6: serotype 2 strains; lanes 7-9: serotype 1/2 strains; lanes 10-12: serotype 9 strains and lanes 13-15: serotype 14 strains.

(B) Ethidium bromide stained agarose gel showing PCR products obtained with tonsillar swabs collected from pigs carrying S. *suis* type 2, type 1 or type 9 strains and *cps2J, cpsII* and *cpsH* primer sets as described in Materials and Methods. Bacterial DNA suitable for PCR was prepared by using the multiscreen methods as described previously (20).

([A]C) *cps[I]II* primers. (B) *cps2J* primers and (C) *cps9H* primers.

Lanes 1-3: PCR products obtained with tonsillar swabs collected from pigs carrying S. *suis* type 1 strains; lanes 4-6: PCR [products] products obtained with tonsillar swabs collected from pigs carrying *S. suis* type 2 strains; lanes 7-9: PCR [prdducts] products obtained with tonsillar swabs collected from pigs carrying S. *suis* type 9 strains; lanes 10-12: PCR products obtained with chromosomal DNA from serotype 9, 2 and 1 strains respectively; lane 13: negative control, no DNA present.

[0076] FIG. 3 illustrates the CPS2 nucleotide sequences and corresponding amino acid sequences from the open reading frames.

[0077] FIG. 4 illustrates the CPS1 nucleotide sequences and corresponding amino acid sequences from the open reading frames.

[0078] FIG. 5 illustrates the CPS9 nucleotide sequences and corresponding amino acid sequences from the open reading frames.

[0079] FIG. 6 illustrates the CPS7 nucleotide sequences and corresponding amino acid sequences from the open reading frames.

[0080] FIG. 7 illustrates alignment of the N-terminal parts of Cps2J and Cps2K.

Identical amino acids are marked by bars. The amino acids shown in bold are also conserved in CPS14I Cps[l]14J of *S. pneumoniae* and several other glycosyltransferases (19). The aspartate residues marked by asterisks are strongly conserved.

[0081] FIG. 8 illustrates transmission electron micrographs of thin sections of various *S. suis* strains.

(A) wild type strain 10;

(B) mutant strain l0cpsB;

(C) mutant strain l0cpsEF.

Bar = l00 nm

[0082] FIG. 9 illustrates the kinetics of phagocytosis of wild type and mutant S. *suis* strains.

(A) Kinetics of phagocytosis of wild type and mutant S. *suis* strains by porcine alveola[i]r macrophages. Phagocytosis was determined as described herein. The Y-axis represents the number of CFU per milliliter in the supernatant fluids as determined by plate counting, the X-axis represents time in minutes.

□ wild type strain 10;

o mutant strain l0cpsB;

Δ mutant strain l0cpsEF.

(B) Kinetics of intracellular killing of wild type and mutant *S. suis* strains by porcine AM. The intracellular killing was determined as described herein. The Y-axis represents the

number of CFU per ml in the supernatant fluids after lysis of the macrophages as determined by plate counting, the X-axis represents time in minutes.

□ wild type strain 10;

o mutant strain l0cpsB;

Δ mutant strain l0cpsEF.

[0083] FIG. 10 illustrates the nucleotide sequence alignment of the highly conserved l00-bp repeated element.

1) 100-bp repeat between cps2G and cps2H

2) 100[—]-bp repeat within "cps2M"

3) 100[—]-bp repeat between cps2O and cps2P

[0084] FIG. 11 illustrates the cps2, cps9 and cps7 gene clusters of S. *suis* serotypes 2, 9 and 7.

(A) Genetic organization of the cps2 gene cluster [84]. The large arrows represent potential ORFs. Gene designations are indicated below the ORFs. Identically filled arrows represent ORFs which showed homology. The small closed arrows indicate the position of the potential promoter sequences. I indicates the position of the potential transcription regulator sequence.

(B) Physical map and genetic organization of the cps9 gene cluster [15]. Restriction sites are as follows: B: *BamHI;* P: *PstI;* H: *HindIII;* X: *XbaI.* The DNA fragments cloned in the various plasmids are indicated. The open arrows represent potential [OREs] ORFs.

(C) Physical map and genetic organization of the [cps7gene]cps7 gene cluster. Restriction sites are as follows: C: *ClaI;* P: *PstI;* Sc: *ScaI.* The DNA fragments cloned in the various plasmids are indicated. The open arrows represent potential OR[E]Fs.

[0085] FIG. 12 illustrates [Ethidium] ethidium bromide stained agarose gel showing PCR products.

(A) Ethidium bromide stained agarose gel showing PCR products obtained with chromosomal DNA of S. *suis* strains belonging to the serotypes 1, 2, 9 and 7 and the cps7H primer set. Strain designations are indicated above the lanes. C: negative control, no DNA present. M: molecular size marker (lambda digested with *EcoRI* and *HindIII).*

(B) Ethidium bromide stained agarose gel showing PCR products obtained with serotype 7 strains collected in different countries and from different organs. Bacterial DNA suitable for PCR was prepared by using the multiscreen method as described herein [89]. Strain designations are indicated above the lanes. M: molecular size marker (lambda digested with *EcoRI* and HindIII).

Detailed Description of the Invention

Experimental part

MATERIAL AND METHODS

Bacterial strains and growth conditions.

[0086] The bacterial strains and plasmids used in this study are listed in Table 1. S. *suis* strains were grown in Todd-Hewitt broth (code CM189, Oxoid), and plated on Columbia agar blood base (code CM331, Oxoid) containing 6% (v/v) horse blood. *E. coli* strains were grown in Luria broth (28) and plated on Luria broth containing 1.5% (w/v) agar. If required, antibiotics were added to the plates at the following concentrations: spectinomycin: 100 ug/ml for S. *suis* and 50 ug/ml for *E. coli* and ampicillin, 50 ug/ml.

[0087] **Serotyping.** The *S. suis* Strains were [serotypes] serotyped by the slide agglutination test with serotype-specific antibodies (44).

[0088] **DNA techniques.** Routine DNA manipulations were performed as described by Sambrook []et al. (36).

[0089] **Alkaline phosphatase activity.** To screen for PhoA fusions in *E. coli,* plasmid libraries were constructed. Therefore, chromosomal DNA of *S. suis* type 2 was digested with *AluI.* The 300-500-bp fragments were ligated to SmaI-digested pPHOS2. Ligation mixtures were transformed to the PhoA$^-$ *E. coli* strain CC118. Transformants were plated on LB media

supplemented with 5-Bromo-4-chloro-3-indolylfosfaat (BCIP, 50 ug/ml, Boehringer, Mannheim, Germany). Blue colonies were purified on fresh LB/BCIP plates to verify the blue phenotype.

[0090] DNA sequence analysis. DNA sequences were determined on a 373A DNA Sequencing System (Applied Biosystems, Warrington, GB). Samples were prepared by using an ABI/PRISM dye terminator cycle sequencing ready reaction kit (Applied Biosystems). Sequencing data were assembled and analyzed using the MacMollyTetra program. Custom-made sequencing primers were purchased from Life Technologies. Hydrophobic stretches within proteins were predicted by the method of Klein []et al. (17). The BLAST program available on Netscape Navigator™ was used to search for protein sequences related to the deduced amino acid sequences.

[0091] Construction of gene-specific knock-out mutants of *S. suis*. To construct the mutant strains 10cpsB and 10cpsEF, we electrotransformed the pathogenic serotype 2 strain 10 (45, 49) of *S. suis* with pCPS11 and pCPS28 respectively. In these plasmids, the *cpsB* and cpsEF genes were disturbed by the insertion of a spectinomycin-resistance gene. To create pCPS11, the internal 400 bp *PstIBamHI* fragment of the *cpsB* gene in pCPS7 was replaced by the Spc^R gene. For this purpose, pCPS7 was digested with *PstI* and BamHI and ligated to the 1,200-bp PstI-*BamHI* fragment, containing the Spc^R gene, from pIC-spc. To construct pCPS28, we have used pIC20R. In this plasmid we inserted the *KpnI-SalI* fragment from pCPS17 (resulting in pCPS25) and the *XbaI-ClaI* fragment from pCPS20 (resulting in pCPS27). pCPS27 was digested with *PstI* and *XhoI* and ligated to the 1,200-bp *PstI-XhoI* fragment, containing the Spc^R gene of pIC-spc. The electrotransformation to *S. suis* was carried out as described before (38).

[0092] Southern blotting and hybridization. Chromosomal DNA was isolated as described by Sambrook []et al. (36). DNA fragments were separated on 0.8% agarose gels and transferred to Zeta-Probe GT membranes (Bio-Rad) as described by Sambrook et al. (36). DNA probes were [labelled] labeled with [(^{-32}P] dCTP (3000 Ci $mmol^{-1}$; Amersham) by use of a random primed labeling kit (Boehringer). The DNA on the blots was hybridized at 65^0C with appropriate DNA probes as recommended by the supplier of the Zeta-Probe membranes. After hybridization, the membranes were washed twice with a solution of 40 mM sodium phosphate, pH 7.2, 1 mM

EDTA, 5% SDS for 30 min at 65°C and twice with a solution of 40 mM sodium phosphate, pH 7.2, 1 mM EDTA, 1% SDS for 30 min at 65°C.

[0093] **PCR.** The primers used in the *cps2J* PCR correspond to the positions 13791-13813 and 14465-14443 in the *S. suis* cps2 locus. The sequences were: 5'-CAAACGCAAGGAATTACGGTATC-3' (SEQ. ID. No. 1) and 5'-GAGTATCTAAAGAATGCCTATTG-3' (SEQ. ID. No. 2). The primers used for the *cpsII* PCR correspond to the positions 4398-4417 and 4839-4821 in the *S. suis cps1* sequence. The sequences were: 5'-GGCGGTCTAGCAGATGCTCG-3' (SEQ. ID. No. 3) and 5' -GCGAACTGTTAGCAATGAC-3' (SEQ. ID. No. 4). The primers used in the *cps9H* PCR correspond to the positions 4406-4126 and 4494-4475 in the *S. suis cps9* sequence. The sequences were: 5'-GGCTACATATAATGGAAGCCC3' (SEQ. ID No. 5) and 5'-CGGAAGTATCTGGGCTACTG-3' (SEQ. ID. No. 6).

[0094] **Construction of gene-specific knock-out mutants of *S. suis*.** To construct the mutant strains 10cpsB and 10cpsEF, we electrotransformed the pathogenic serotype 2 strain 10 of *S. suis* with pCPS11 and pCPS28 respectively. In these plasmids, the *cpsB* and cpsEF genes were disturbed by the insertion of a spectinomycin-resistance gene. To create pCPS11, the internal 400 bp *PstI-BamHI* fragment of the *cpsB* gene in pCPS7 was replaced by the Spc^R gene. For this purpose, pCPS7 was digested with *PstI* and BamHI and ligated to the 1,200-bp *PstI-BamHI* fragment, containing the Spc^R gene, from pIC-spc. To construct pCPS28, we have used pIC20R. In this plasmid, we inserted the *KpnI-SalI* fragment from pCPS17 (resulting in pCPS25) and the *XbaI-ClaI* fragment from pCPS20 (resulting in pCPS27). pCPS27 was digested with *PstI* and *XhoI* and ligated to the 1,200-bp *PstI-XhoI* fragment, containing the Spc^R gene of pIC-spc. The electrotransformation to *S. suis* was carried out as described before (38).

[0095] **Phagocytosis assay.** Phagocytosis assays were performed as described by Leij []et al. (23). Briefly, to opsonize the cells, 10^7 *S. suis* cells were incubated with 6% SPF-pig serum for 30 min at 37°C in a head-over-head rotor at 6 rpm. 10^7 AM and 10^7 opsonized *S. suis* cells were combined and incubated at 37°C under continuous rotation at 6 rpm. At 0, 30, 60 and 90 min, 1- ml samples were collected and mixed with 4 ml of ice-cold EMEM to stop phagocytosis. Phagocytes were removed by centrifugation for 4 min at 110 x g and 4°C. The number of colony-

forming units, ([CFU]"CFU") in the supernatants was determined. Control experiments were carried out simultaneously by combining 10^7 opsonized S. *suis* cells with EMEM (without AM).

[0096] Killing assays. AM (10^7/ml) and opsonized *S. suis* cells (10^7/ml) were mixed 1:1 and incubated for 10 min at 37°C under continuous rotation at 6 rpm. Ice-cold EMEM was added to stop further phagocytosis and killing. To remove extracellular *S. suis* cells, phagocytes were washed twice (4 min, 110 x g, 4°C) and resuspended in 5 ml EMEM containing 6% SPF serum. The tubes were incubated at 37°C under rotation at 6 rpm. After 0, 15, 30, 60 and 90 min, samples were collected and mixed with ice-cold EMEM to stop further killing. The samples were centrifuged for 4 min at 110 x g at 4°C and the phagocytic cells were lysed in EMEM containing 1% saponine for 20 min at room temperature. The number of CFU in the suspensions was determined.

[0097] Pigs. Germfree pigs, cross[-]breeds of Great Yorkshire and Dutch [l]Landrace, were obtained from sows by caesarian sections. The surgery was performed in sterile flexible film isolators. Pigs were allotted to groups, each consisting of 4 pigs, and were housed in sterile stainless steel incubators.

[0098] Experimental infections. Pigs were inoculated intranasally with *S. suis* type 2 as described before. To predispose the pigs for infection with *S. suis*, five-day old pigs were inoculated intranasally with about 10^7 CFU of *Bordetella bronchiseptica* strain 92932. Two days later, the pigs were inoculated intranasally with *S. suis* type 2 (10^6 CFU). Pigs were monitored twice daily for clinical signs of disease, such as fever, nervous signs and lameness. Blood samples were collected three times a week from each pig. White blood cells were counted with a cell counter. To monitor infection with *S. suis* and *B. bronchiseptica* and to check for absence of contaminants, we collected swabs of nasopharynx and feces daily. The swabs were plated directly onto Columbia agar containing 6% horse blood. After three weeks, the pigs were killed and examined for pathological changes. Tissue specimens from the central nervous system, serosae, and joints were examined bacteriologically and histologically as described herein (45, 49). Colonization of the serosae was scored positively when *S. suis* was isolated from the pericardium, thoracal pleura or the peritoneum. Colonization of the joints was scored positively when *S. suis* was isolated from one or more joints (12 joints per animal were scored).

[0099] **Vaccination and challenge.** One week old pigs were vaccinated intravenously with a dosage of 106 cfu of the *S. suis* strains 10cpsEF or 10cpsB. Three weeks later, the pigs were challenged intravenously with the pathogenic Serotype 2 strain 10 (107 cfu). Disease monitoring, [haematologicl]hematological, serological and bacteriological examinations as well as post-mortum examinations were as described before under experimental infections.

[0100] **Electron Microscopy.** Bacteria were prepared for electron microscopy as described by Wagenaar []et al. (50). Shortly, bacteria were mixed with agarose MP (Boehringer) of 37° C to a concentration of 0.7%. The mixture was immediately cooled on ice. Upon gelifying, samples were cut into 1 to 1.5 mm slices and incubated in a fixative containing 0.8% glutaraldehyde and 0.8% osmiumtetraoxide. Subsequently, the samples were fixed and stained with uranyl acetate by microwave stimulation, dehydrated and imbedded in eponaraldite resin. Ultra-thin sections were counterstained with lead citrate and examined with a Philips CM 10 electron microscope at 80 kV (FIG. 8).

[0101] **Isolation of porcine alveolar macrophages (AM).** Porcine AM were obtained from the lungs of specific pathogen free ([SPF]"SPF") pigs. Lung lavage samples were collected as described by van Leengoed et al. (43). Cells were suspended in EMEM containing 6% (v/v). SPF-pig serum and adjusted to 10^7 cells per ml.

RESULTS

Identification of the cps locus.

[0102] The *cps* locus of *S. suis* type 2 was identified through [by making use of] a strategy developed for the genetic identification of exported proteins (13, 31). In this system, we used a plasmid (pPHOS2) containing a truncated alkaline phosphatase gene (13). The gene lacked the promoter sequence, the translational start site and the signal sequence. The truncated gene is preceded by a unique SmaI restriction site. Chromosomal DNA of *S. suis* type 2, digested with *AluI,* was randomly cloned in this restriction site. Because translocation of PhoA across the cytoplasmic membrane of *E. coli* is required for enzymatic activity, the system can be used to select for *S. suis* fragments containing a promoter sequence, a translational start site and a functional signal sequence. Among 560 individual *E. coli* clones tested, 16 displayed a dark blue

phenotype when plated on media containing BCIP. DNA sequence analysis of the inserts from several of these plasmids [were] was performed (results not shown) and the deduced amino acid sequences were analyzed. The hydrophobicity profile of one of the clones (pPHOS7, results not shown) showed that the N-terminal part of the sequence resembled the characteristics of a typical signal peptide: a short hydrophilic N-terminal region is followed by a hydrophobic region of 38 amino acids. These data indicate that the phoA system was successfully used for the selection of *S. suis* genes encoding exported proteins. Moreover, the sequences were analyzed for similarities present in the databases. The sequence of pPHOS7 showed a high similarity (37% identity) with the protein encoded by the *cps14C* gene of *Streptococcus pneumoniae* (19). This strongly suggests that pPHOS7 contains a part of the *cps* operon of *S. suis* type 2.

[0103] Cloning of the flanking *cps* genes. In order to clone the flanking *cps* genes of *S. suis* type 2, the insert of pPHOS7 was used as a probe to identify chromosomal DNA fragments which contain flanking *cps* genes. A 6-kb *HindIII* fragment was identified and cloned in pKUN19. This yielded clone pCPS6 (FIG. 1, part C). Sequence analysis of the insert of pCPS6 revealed that pCPS6 most probably contained the 5'-end of the *cps* locus, but still lacked the 3'-end. Therefore, sequences of the 3'-end of pCPS6 were in turn used as a probe to identify chromosomal fragments containing *cps* sequences located further downstream. These fragments were also cloned in pKUN19, resulting in pCPS17. Using the same system of chromosomal walking, we subsequently generated the plasmids pCPS18, pCPS20, pCPS23 and pCPS26, containing downstream *cps* sequences.

[0104] Analysis of the cps operon. The complete nucleotide sequence of the cloned fragments was determined (FIG. 4). Examination of the compiled sequence revealed the presence of at least 13 potential open reading frames (Orfs), which were designated as Orf 2Y, Orf2X and Cps2A-Cps2K (FIG. 1, part A; FIG. 1, part A). Moreover, a 14th, incomplete[,] Orf (Orf 2Z) was located at the 5'-end of the sequence. Two potential promoter sequences were identified. One was located 313 bp (locations 1885-1865 and 1884-1889) upstream of Orf2X. The other potential promoter sequence was located 68 bp upstream of Orf2Y (locations 2241-2236 and 2216-2211). Orf2Y is expressed in opposite orientation. Between Orfs 2Y and 2Z, the sequence contained a potential stem-loop structure, which could act as a transcription terminator. Each Orf is preceded

by a ribosome-binding site and the majority of the Orfs are very closely linked. The only significant intergenic gap was found between Cps2G and Cps2H (389 nucleotides). However, no obvious promoter sequences or potential stem-loop structures were found in this region. These data suggest that Orf2X and Cps2A-Cps2K are arranged as an operon.

[0105] An overview of all Orfs with their properties is shown in Table 2. The majority of the predicted gene products is related to proteins involved in polysaccharide biosynthesis. Orf2Z showed some similarity with the YitS protein of *Bacillus subtilis.* YitS was identified during the sequence analysis of the complete genome of B. *subtilis.* The function of the protein is unknown.

[0106] Orf2Y showed similarity with the YcxD protein of *B. subtilis* (53). Based on the similarity between YcxD and MocR of *Rhizobium meliloti* (33), YcxD was suggested to be a regulatory protein.

[0107] Orf2X showed similarity with the hypothetical YAAA proteins of *Haemophilus influenzae* and *E. coli.* The function of these proteins is unknown.

[0108] The gene products encoded by the *cps2A, cps2B, cps2C* and *cps2D* genes showed approximate similarity with the CpsA, CpsC, CpsD and CpsB proteins of several serotypes of *Streptococcus pneumoniae* (19), respectively. This suggests similar functions for these proteins. Hence, Cps2A may have a role in the regulation of the capsular polysaccharide synthesis. Cps2B and Cps2C could be involved in the chain length determination of the type 2 capsule and Cps2C can play an additional role in the export of the polysaccharide. The Cps2D protein of *S. suis* is related to the CpsB protein of *S. pneumoniae* and to proteins encoded by genes of several other Gram-positive bacteria involved in polysaccharide or exopolysaccharide synthesis, but their function is unknown (19).

[0109] The protein encoded by the *cps2E* gene showed similarity to several bacterial proteins with [glycosyl transferase]glycosyltransferase activities Cps14E and Cps19fE of *S. pneumoniae* serotypes 14 and 19F (18, 19, 29), CpsE of *Streptococcus salvarius* (X94980) and CpsD of *Streptococcus agalactiae* (34). Recently, Kolkman et al. (18) showed that Cps14E is a glucosyl-1-phosphate transferase that links glucose to a lipid carrier, the first step in the

biosynthesis of the *S. pneumoniae* type 14 repeating unit. Based on these data, a similar function may be fulfilled by Cps2E of *S. suis*.

[0110] The protein encoded by the *cps2F* gene showed similarity to the protein encoded by the *rfbU* gene of *Salmonella enteritica.* (25). This similarity is most pronounced in the C-terminal regions of these proteins. The *rfbU* gene was shown to encode[d] mannosyltransferase activity (25).

[0111] The *cps2G* gene encoded a protein that showed moderate similarity with the *rfbF* gene product of *Campylobacter hyoilei* (22), the *epsF* gene product of *S. thermophilus* (40) and the *capM* gene product of *S. aureus* (24). On the basis of similarity, the *rfbF, epsF* and *capM* genes are suggested to encode[d] galactosyltransferase activities. Hence, a similar [glycosyl transferase]glycosyltransferase activity could be fulfilled by the *cps2G* gene product.

[0112] The *cps2H* gene encodes a protein that is similar to the N-terminal region of the *lgtD* gene product of *Haemophilus influenzae* (U32768). Moreover, the hydrophobicity plots of Cps2H and LgtD looked very similar in these regions (data not shown). Based on sequence similarity, the *lgtD* gene product was suggested to have [glycosyl transferase]glycosyltransferase activity (U32768).

[0113] The gene product encoded by the *cps2I* gene showed some similarity with a protein of *Actinobacillus actinomycetemcomitans* (AB002668). This protein is part of the gene cluster responsible for the serotype-b-specific antigen of *A. actinomycetemcomitans.* The function of the protein is unknown.

[0114] The gene products encoded by the *cps2J* and *cps2K* genes showed significant similarities to the Cpsl4J protein of *S. pneumoniae.* The *cps14J* gene of *S. pneumoniae* was shown to encode a β-1,4-galactosyltransferase activity. In *S. pneumoniae*, CpsJ is responsible for the addition of the fourth (*i.e.* last) sugar in the synthesis of the *S. pneumoniae* serotype 14 polysaccharide (20). Even some similarity was found between Cps2J and Cps2K (FIG. 2, 25.5% similarity). This similarity was most pronounced in the N-terminal regions of the proteins (FIG. 7). Recently, two small conserved regions were identified in the N-terminus of Cps14J and Cps14I and their homologues (20). These regions were predicted to be important for catalytic activity. Both regions, DXS and DXDD [Fig.] (FIG. 2), were also found in Cps2J and Cps2K.

[0115] **Distribution of the *cps2* genes in other *S. suiss* serotypes.** To examine the relationship between the *cps2* genes and *cps* genes in the other *S. suis* serotypes, we performed crosshybridization experiments. DNA fragments of the individual *cps2* genes were amplified by PCR, labeled with ^{32}P, and used to probe Southern blots of chromosomal DNA of the reference strains of the 35 different *S. suis* serotypes. Large variations in the hybridization patterns were observed (Table 4). As a positive control, we used a probe specific for 16S rRNA. The 16S rRNA probe hybridized with all serotypes tested. However, none of the other genes tested were common in all serotypes. Based on the genetic organization of the genes, we previously suggested that *orfX* and *cpsA-cpsK* genes are part of one operon and that the proteins encoded by these genes are all involved in polysaccharide biosynthesis. OrfY and OrfZ are not a part of this operon, and their role in the polysaccharide biosynthesis is unclear. Based on sequence similarity data, OrfY may be involved in regulation of the *cps2* genes. OrfZ is proposed to be unrelated to polysaccharide biosynthesis. Probes specific for the *orfZ, orfY, orfX, cpsA, cpsB, cpsC* and *cpsD* genes hybridized with most other serotypes. This suggests that the proteins encoded by these genes are not type-specific, but may perform more common functions in biosynthesis of the capsular polysaccharide. This confirms previous data which showed that the *cps2A-cps2D* genes showed strong similarity to *cps* genes of several serotypes of *Streptococcus pneumoniae*. Based on this similarity, Cps2A is possibly a regulatory protein, whereas Cps2B and Cps2C may play a role in length determination and export of polysaccharide. The *cps2E* gene hybridized with DNA of Serotypes 1, 2, 14 and 1/2. The *cps2E* gene showed a strong similarity to the *cps14E* gene of *S. pneumoniae* (18). This enzyme was shown to have a glucosyl-1-phosphate activity and catalyzed the transfer of glucose to a lipid carrier (18). These data indicate that a glycosyltransferase closely related to Cps14E may be responsible for the first step in the biosynthesis of polysaccharide in the *S. suis* serotypes 1, 2, 14 and 1/2. The *cps2F, cps2G, cps2H, cps2I* and *cps2J* genes hybridized with chromosomal DNA of serotypes 2 and 1/2 only. The *cps2G* gene showed an additional weak hybridization signal with DNA of serotype 34. In agglutination tests, serotype 1/2 showed agglutination with sera specific for serotype 2 as well as with sera specific for serotype 1. This suggests that serotype 1/2 shares antigenic determinants with both types 1 and 2. The hybridization data confirmed these data. All putative glycosyltransferases present in serotype 2 are also present in serotype 1/2. The *cps2K*

gene showed a [similar]hybridization pattern [as]similar to the *cps2E* gene. Hybridization was observed with DNA of serotypes 1, 2, 14 and 1/2. Taken together, these hybridization data show that the *cps2* gene cluster can be divided into three regions: a central region containing the type-specific genes is flanked by two regions containing common genes for various serotypes.

[0116] Cloning of the type-specific *cps* genes of serotypes 1 and 9. To clone the type-specific *cps* genes of *S. suis* serotype 1, we used the *cps2E* gene as a probe to identify chromosomal DNA fragments of type 1 which contain flanking *cps* genes. A 5 kb *EcoRV* fragment was identified and cloned in pKUN19. This yielded pCPS1-1 (FIG. 1, part B). This fragment was in turn used as a probe to identify an overlapping 2.2 kb HindIII fragment. pKUN19 containing this HindIII fragment was designated pCPS1-2. The same strategy was followed to identify and clone the type-specific *cps* genes of serotype 9. In this case, we used the *cps2D* gene as a probe. A 0.8 kb HindIII-XbaI fragment was identified and cloned, yielding pCPS9-1 (FIG. 1, part C). This fragment was in turn used as a probe to identify a 4 kb XbaI fragment. pKUN19 containing this 4 kb XbaI fragment was designated pCPS9-2.

[0117] Analysis of the cloned *cps1* genes. The complete nucleotide sequence of the inserts of pCPS1-1 and pCPS1-2 was determined (FIG. 5). Examination of the sequence revealed the presence of five complete and two incomplete Orfs (FIG.1, part B). Each Orf is preceded by a ribosome-binding site. In accord with data obtained for the *cps2* genes of serotype 2, the majority of the Orfs is very closely linked. The only significant gap (718 bp) was found between Cps1G and Cps1H. No obvious promoter sequences or potential stem-loop structures could be found in this region. This suggests that, as in serotype 2, the *cps* genes in serotype 1 are arranged in an operon.

[0118] An overview of the Orfs and their properties [in] is shown in Table 2. As expected on the basis of the hybridization data (Table 4), the protein encoded by the *cps1E* gene was related to Cps2E of *S. suis* type 2 (identity of 86%). The fragment cloned in pCPS1-1 lacked the coding region for the first 7 amino acids of the *cps1E* gene.

[0119] The protein encoded by the *cps1F* and *cps1G* genes showed strong similarity to the Cps14F and Cps14G proteins of *Streptococcus pneumoniae* serotype 14, respectively (20). The function of the Cps14F is not completely clear, but it has been suggested that Cps14F [can

enhance]has a role in glycosyltransferase activity. The *cps14G* gene of *S. pneumoniae* was shown to encode β-1, 4-galactosyltransferase activity. In *S. pneumoniae* type 14, this activity is required for the second step in the biosynthesis of the oligosaccharide subunit (20). Based on the similarity of the data, similar glycosyltransferase and enhancing activities are suggested for the [cps 1G]cps1G and *cps1F* genes of *S. suis* type 1.

[0120] The protein encoded by the *cps1H* gene showed similarity to the Cps14M protein of *S. pneumoniae* (20). Based on sequence similarity, Cps14H was proposed to be the polysaccharide polymerase (20).

[0121] The protein encoded by the *cps1I* gene showed some similarity with the Cps14J protein of *S. pneumoniae* (19). The *cps14J* gene was shown to encode a β-1, 4-galactosyltransferase activity, responsible for the addition of the fourth (*i.e.* last) sugar in the synthesis of the *S. pneumoniae* serotype 14 polysaccharide.

[0122] Between Cps1G and Cps1H, a gap of 718 bp was found. This region revealed three small Orfs. The three Orfs were expressed in three different reading frames and were not preceded by potential ribosome binding sites, nor contained potential start sites. However, the three potential gene products encoded by this region showed some similarity with three successive regions of the C-terminal part of the EpsK protein of *Streptococcus thermophilus* (27% identity, 40). The region related to the first 82 amino acids is lacking.

[0123] **Analysis of the cloned *cps9* genes.** We also determined the complete nucleotide sequence of the inserts of pCPS9-1 and pCPS9-2 (FIG. 6). Examination of the sequence revealed the presence of three complete and two incomplete Orfs (FIG.1, part C). As in serotypes 1 and 2, all Orfs are preceded by a ribosome-binding site and are very closely coupled. As suggested by the hybridization data (Table 4), the Cps2D and Cps9D proteins were highly related (Table 2). Based on sequence comparisons, pCPS9-1 lacked the first 27 amino acids of the Cps9D protein.

[0124] The protein encoded by the *cps9E* gene showed some similarity with the CapD protein of *Staphylococcus aureus* serotype 1 (24). Based on sequence similarity data, the Cap1D protein was suggested to be an epimerase or a dehydratase involved in the synthesis of N-acetylfructosamine or N-acetylgalactosamine (63).

[0125] Cps9F showed some similarity to the CapM proteins of *S. aureus* serotypes 5 and 8 (61, 64, 65). Based on sequence similarity data, Cap5M and Cap8M are proposed to be glycosyltransferases (63).

[0126] The protein encoded by the *cps9G* gene showed some similarity [with] to a protein of *Actinobacillus actinomycetemcomitans* (AB002668_4). This protein is part of a gene cluster responsible for the serotype-b specific antigens of *Actinobacillus actinomycetemcomitans.* The function of the protein is unknown.

[0127] The protein encoded by the *cps9H* gene showed some similarity [with] to the *rfbB* gene of *Yersinia enterolitica* (68). The RfbB protein was shown to be essential for O-antigen synthesis, but the function of the protein in the synthesis of the 0:3 lipopolysaccharide is unknown.

[0128] **Serotype 1 and serotype 9 specific *cps* genes.** To determine whether the cloned fragments in pCPS1-1, pCPS1-2, pCPS9-1 and pCPS9-2 contained the type-specific genes for serotype 1 and 9, respectively, cross[ ]-hybridization experiments were performed. DNA fragments of the individual *cps1* and *cps9* genes were amplified by PCR, labeled with ^{32}P, and used to probe Southern blots of chromosomal DNA of the reference strains of the 35 different *S. suis* serotypes. The results are shown in Table 5. Based on the data obtained with the *cps2E* probe (Table 4), the *cps1E* probe was expected to hybridize with chromosomal DNA of *S. suis* serotypes 1, 2, 14, 27 and 1/2. The *cps1H, cps9E* and *cps9F* probes hybridized with most other serotypes. However, the *cps1F* and *cps1G* and cps1I probes hybridized with chromosomal DNA of serotypes 1 and 14 only. The *cps9G* and *cps9H* probes hybridized with serotype 9 only. These data suggest that the *cps9G* and *cps9H* probes are specific for serotype 9 and, therefore, could be useful tools for the development of rapid and sensitive diagnostic tests for *S. suis* type 9 infections.

[0129] **Type specific PCR.** So far, the probes were tested on the 35 different reference strains only. To test the diagnostic value of the typespecific *CpS* probes further, several other *S. suis* serotype 1, 2, 1/2, 9 and 14 strains were used. Moreover, since a PCR[ ]-based method would be even more rapid and sensitive than a hybridization test, we tested whether we could use a PCR for the serotyping of the *S. suis* strains. The oligonucleotide primer sets were chosen within the *cps2J, cps1I* and *cps9H* genes. Amplified fragments of 675 bp, 380 bp and 390 bp were expected, respectively. The results show that 675 bp fragments were amplified on type 2 and 1/2

strains using *cps2J* primers; 380 bp fragments were amplified on type 1 and 14 strains using *cps1I* primers and 390 bp fragments were amplified on type 9 strains using *cps9H* primers.

[0130] Construction of mutants impaired in capsule production. To evaluate the role of the capsule of *S. suis* type 2 in[the] pathogenesis, we constructed two isogenic mutants in which capsule production was disturbed. To construct mutant 10cpsB, pCPS11 was used. In this plasmid, a part of the *cps2B* gene was replaced by the spectinomycin-resistance gene. To construct mutant strain 10cpsEF, the plasmid pCPS28 was used. In pCPS28, the 3'-end of *cps2E* gene, as well as the 5'-end, of *cps2F* gene, were replaced by the spectinomycin-resistance gene. pCPS11 and pCPS28 were used to electrotransform strain 10 of *S. suis* type 2 and spectinomycin-resistant colonies were selected. Southern blotting and hybridization experiments were used to select double [cross over]crossover integration events (results not shown). To test whether the capsular structure of the strains 10cpsB and 10cpsEF was disturbed, we used a slide agglutination test using a suspension of the mutant strains in hyperimmune anti-[S. suis] *S. suis* type 2 serum (44). The results showed that even in the absence of serotype specific antisera, the bacteria agglutinated. This indicates that, in the mutant strains, the capsular structure was disturbed. To confirm this, thin sections of wild type and mutant strains were compared by electron microscopy. The results showed that, compared to the wild type (FIG. 3, part A), the amount of capsule produced by the mutant strains was greatly reduced (FIG. 3, part B and part C). Almost no capsular material could be detected on the surface of the mutant strains.

[0131] Capsular mutants are sensitive to phagocytosis and killing by porcine alveolar macrophages ("PAM"). The capsular mutants were tested for their ability to resist phagocytosis by PAM in the presence of porcine SPF serum. The wild type strain 10 seemed to be resistant to phagocytosis under these conditions (FIGs. 9A and 9B). In contrast, the mutant strains were efficiently ingested by macrophages (FIGs. 9A and 9B). After 90 min., more than 99.7% (strain 10cpsB) and 99.8% (strain 10cpsEF) of the mutant cells were ingested by the macrophages. Moreover, as shown in FIGs. 9A and 9B the ingested strains were efficiently killed by the macrophages. 90-98% of all ingested cells were killed within 90 min. No differences could be observed between wild type and mutant strains. These data indicate that the capsule of *S. suis* type 2 efficiently protects the organism from uptake by macrophages *in vitro*.

[0132] **Capsular mutants are less virulent for germfree piglets.** The virulence properties of the wild-type and mutant strains were tested after experimental infection of newborn germfree pigs (45, 49). Table 1 shows that specific and nonspecific signs of disease could be observed in all pigs inoculated with the wild type strain. Moreover, all pigs inoculated with the wild type strain died during the course of the experiment or were killed because of serious illness or nervous disorders (Table 3). In contrast, the pigs inoculated with strains 10cpsB and 10cpsEF showed no specific signs of disease and all pigs survived until the end of the experiment (Table 6). The temperature of the pigs inoculated with the wild type strain increased 2 days after inoculation and remained high until day 5 (Table 3). The temperature of the pigs inoculated with the mutant strains sometimes exceeded[the] 40^0C, however, we could observe significant differences in the fever index (*i.e.* percent of observations in an experimental group during which pigs showed fever (>40^0C)) between pigs inoculated with wild type and mutant strains. All pigs showed increased numbers of polymorphonuclear leucocytes (PMLs) (>10 x 10^9 PMLs per litre) (Table 3). However, in pigs inoculated with the mutant strains, the percentage of samples with increased numbers of PMLs was considerably lower. *S. suis* strains and *B. bronchiseptica* could be isolated from the nasopharynx and feces swab samples of all pigs from 1 day post-infection until the end of the experiment (Table 3). Postmortem, the wild type strain could frequently be isolated from the central nervous system ([CNS]"CNS"), kidney, heart, liver, spleen, serosae, joints and tonsils. Mutant strains could easily be recovered [form] from the tonsils, but were never recovered from the kidney, liver or spleen. Interestingly, low numbers of the mutant strains were isolated from the CNS, the serosae, the joints, the lungs and the heart. Taken together, these data strongly indicated that mutant *S. suis* strains, impaired in capsule production, are not virulent for young germfree pigs.

[0133] We describe the identification and the molecular characterization of the *cps* locus, involved in the capsular polysaccharide biosynthesis, of *S. suis*. Most of the genes seemed to belong to a single transcriptional unit, suggesting a co[-]ordinate control of these genes. We assigned functions to most of the gene products. We thereby identified regions involved in regulation (Cps2A), chain length determination (Cps2B, C), export (Cps2C) and biosynthesis (Cps2E, F, G, H, J, K). The region involved in biosynthesis is located at the center of the gene

cluster and is flanked by two regions containing genes with more common functions. The incomplete *orf2Z* gene was located at the 5'-end of the cloned fragment. Orf2Z showed some similarity with the YitS protein of *B. subtilis.* However, because the function of the YitS protein is unknown, this did not give us any information about the possible function of Orf2Z. Because the *orf2Z* gene is not a part of the *cps* operon, a role of this gene in polysaccharide biosynthesis is not expected. The Orf2Y protein showed some similarity with the YcxD protein of *B.subtilis* (53). The YcxD protein was suggested to be a regulatory protein. Similarly, Orf2Y may be involved in the regulation of polysaccharide biosynthesis. The Orf2X protein showed similarity with the YAAA proteins of *H. influenzae* and *E. coli.* The function of these proteins is unknown. In *S. [suis] suis* type 2, the *orf2X* gene seemed to be the first gene in the *cps2* operon. This suggests a role of Orf2X in the polysaccharide biosynthesis. In *H. influenzae* and *E. coli,* however, these proteins are not associated with capsular gene clusters. The analysis of isogenic mutants impaired in the expression of Orf2X should give more insight in the presumed role of Orf2X in the polysaccharide biosynthesis of *S. suis* type 2.

[0134] The gene products encoded by the *cps2E, cps2F, cps2G, cps2H, cps2J* and *cps2K* genes showed little similarity with glycosyltransferases of several Gram-positive or Gram-negative bacteria (18, 19, 20, 22, 25). The *cps2E* gene product shows some similarity with the Cps14E protein of *S. pneumoniae* (18, 19). Cps14E is a glucosyl-1-phosphate transferase that links glucose to a lipid carrier (18). In *S. pneumoniae,* this is the first step in the biosynthesis of the oligosaccharide repeating unit. The structure of the *S. suis* serotype 2 capsule contains glucose, galactose, rhamnose, N-acetyl glucos[e]amine and sialic acid in a ratio of 3:1:1:1:1 (7). Based on these data, we conclude that Cps2E of *S. suis* has glucosyltransferase activity[,] and is involved in the linkage of the first sugar to the lipid carrier.

[0135] The C-terminal region of the *cps2F* gene product showed some similarity with the RfbU of *Salmonella enteritica.* RfbU was shown to have mannosyltransferase activity (24). Because mannosyl is not a component of the *S. suis* type 2[,] polysaccharide, a mannosyltransferase activity is not expected in this organism. Nevertheless, *cps2F* encodes a glycosyltransferase with another sugar specificity.

[0136] Cps2G showed moderate similarity to a family of gene products suggested to encode galactosyltransferase activities (22, 24, 40). Hence, a similar activity is shown for Cps2G.

[0137] Cps2H showed some similarity with LgtD of *H. influenzae* (U32768). Because LgtD was proposed to have glycosyltransferase activity[ ], a similar activity is fulfilled by Cps2H.

[0138] Cps2J and Cps2K showed similarity to Cps14J of *S. pneumoniae* (20). Cps2J showed similarity with Cps14I of *S. pneumoniae* as well. Cps14I was shown to have N-acetyl glucosaminyltransferase activity, whereas Cps14J has a β-1, 4-galactosyltransferase activity (20). In *S. pneumoniae,* Cps14I is responsible for the addition of the third sugar and Cps14J for the addition of the last sugar in the synthesis of the type 14 repeating unit (20). Because the capsule of *S. suis* type 2 contains galactose as well as N-acetyl glucosamine components, galactosyltransferase as well as N-acetyl glucoaminyltransferase activities could be envisaged for the *cps2J* and *cps2K* gene products, respectively. As was observed for Cps14I and Cps14J, the N-termini of Cps2J and Cps2K showed a significant degree of sequence similarity. Within the N-terminal domains of Cps14I and Cps14J, two small regions were identified, which were also conserved in several other glycosyltransferases (22). Within these two regions, two Asp residues were proposed to be important for catalytic activity. The two conserved regions, DXS and DXDD, were also found in Cps2J and Cps2K.

[0139] The function of Cps2I remains unclear. Cps2I showed some similarity with a protein of *A. actinomycetemcomitans.* Although this protein part is of the gene cluster responsible for the serotype-B-specific antigens, the function of the protein is unknown.

[0140] We further describe the identification and characterization of the *cps* genes specific for *S. suis* serotypes 1, 2 and 9. After the entire *cps2* locus of *S. suis* serotype 2 was cloned and characterized, functions for most of the *cps2* gene products could be assigned by sequence homologies. Based on these data, the glycosyltransferase activities, required for type specificity, could be located in the center of the operon. Cross-hybridization experiments, using the individual *cps2* genes as probes on chromosomal DNAs of the 35 different serotypes, confirmed this idea. The regions containing the type-specific genes of serotypes 1 and 9 could be cloned and characterized, showing that an identical genetic organization of the *CpS* operons of other *S. suis* serotypes exists. The *cps1E, cps1F, cps1G, cps1H,* and *cps1I* genes revealed a

striking similarity with [*cps14 E*]*cps14E, cps14F, cps14G, cps14H* and *cps14J* genes of *S. pneumoniae*. Interestingly, *S. pneumoniae* serotype 14 is the serotype most commonly associated with pneumococcal infections in young children (54), whereas *S. suis* serotype 1 strains are most commonly isolated from piglets younger than 8 weeks (46). In *S. pneumoniae*, the *cps14E, cps14G, cps14I* and *cps14J* encode the glycosyltransferases required for the synthesis of the type 14 tetrameric repeating unit, showing that the *cps1E, cps1G* and *cps1I* genes encoded glycosyltransferases. The precise functions of these genes as well as the substrate specificities of the enzymes can be established. In *S. pneumoniae*, the *cps14E* gene was shown to encode a glucosyl-1-phosphate transferase catalyzing the transfer of glucose to a lipid carrier. Moreover, *cpsE*-like genes were found in *S. pneumoniae* serotypes 9N, 13, 14, 15B, 15C, 18F, 18A and 19F (60). *CpsE* mutants were constructed in the serotypes 9N, 13, 14 and 15B. All mutant strains lacked glucosyltransferase activity (60). Moreover, in all these *S. pneumoniae* serotypes, the *cpsE* gene seemed to be responsible for the addition of glucose to the lipid carrier. Based on these data, we suggest that in *S. suis* type 1, the *cps1E* gene may fulfil a similar function. The structure of the *S. suis* type 1 capsule is unknown, but it is composed of glucose, galactose, N-acetyl glucosamine, N-acetyl galactosamine and sialic acid in a ratio of 1: 2.4: 1: 1:1.4 (5). Therefore, a role of a *cpsE*-like glucosyltransferase activity can easily be envisaged. *[CpsE like]* CpsE-like sequences were also found in serotypes 2, 1/2 and 14.

[0141] For polysaccharide biosynthesis in *S. pneumoniae* type 14, transfer of the second sugar of the repeating unit to the first lipid-linked sugar is performed by the gene products of *cps14F* and *cps14G* (20). Similar to Cps14F and Cps14G, the *S. suis* type 1 proteins Cps1F and Cps1G may act as one glycosyltransferase performing the same reaction. Cps14F and Cps14G of *S. pneumoniae* showed similarity to the N-terminal half and C-terminal half of the SpsK protein of *Sphingomonas* (20, 67), respectively. This suggests a combined function for both proteins. Moreover, *cps14F*-and *cps14G*-like sequences were found in several serotypes of *S. pneumoniae* and these genes always seemed to exist together (60). The same was observed for *S. suis* type 1. The *cps1F* and *cps1G* probes hybridized with type 1 and type 14 strains.

[0142] According to the similarity found between the *cps1H* gene and the *cps14H* gene of *S. pneumoniae* (20), *cps1H* is expected to encode a polysaccharide polymerase.

[0143] The protein encoded by the *cps1I* gene showed some similarity with the Cps14J protein of *S. pneumoniae* (19). The *cps14J* gene was shown to encode a β-1, 4-galactosyltransferase activity, responsible for the addition of the fourth (*i.e.* last) sugar in the synthesis of the *S. pneumoniae* serotype 14 polysaccharide. In *S. suis* type 2, the proteins encoded by the *cps2J* and *cps2K* genes showed similarity to the Cps14J protein. However, no significant homologies were found between Cps2J, Cps2K and Cps1I. In the N-terminal regions of Cps14J and Cps14I, two small conserved regions, DXS and DXDD, were identified (19). These regions seemed to be important for catalytic activity (13). At the same positions in the sequence, Cps2I contained the regions DXS and DXED.

[0144] In the region between Cps1G and Cps1H, three small Orfs were identified. Since the Orfs were expressed in three different reading frames, and did not contain potential start sites, expression is not expected. However, the three potential gene products encoded by this region showed some similarity with three successive regions of the C-terminal part of the EpsK protein of *Streptococcus thermophilus* (27% identity, 40). The region related to the first 82 amino acids is lacking. The EpsK protein was suggested to play a role in the export of the exopolysaccharide by rendering the polymerized exopolysaccharide more hydrophobic through a lipid modification. These data could suggest that the sequences in the region between Cps1G and Cps1H originated from epsK-like sequence. Hybridization experiments showed that this *epsK*-like region is also present in other serotype 1 strains as well as in serotype 14 strains (results not shown).

[0145] The function of most of the cloned serotype 9 genes can be established. Based on sequence similarity data, the *cps9E* and *cps9F* genes could be glycosyltransferases (61, 24, 63, 64, 65). Moreover, the *cps9G* and *cps9H* genes showed similarity to genes located in regions involved in polysaccharide biosynthesis, but the function of these genes is unknown (68).

[0146] Cross-hybridization experiments using the individual *cps2, cps1* and *cps9* genes as probes[,] showed that the *cps9G* and *cps9H* probes specifically hybridized with serotype 9 strains.

[0147] Therefore, these are useful as tools for the identification of *S. suis* type 9 strains both for diagnostic purposes as well as in epidemiological and transmission studies. We previously

developed a PCR method which can be used to detect *S. suis* strains in nasal and tonsil swabs of pigs (62). The method was used to identify pathogenic (EF-positive) strains of *S. suis* serotype 2. Besides *S. suis* type 2 strains, serotype 9 strains are frequently isolated from organs of diseased pigs. However, until now, a rapid and sensitive diagnostic test was not available for type 9 strains. Therefore, the type 9 specific probes or the type 9 specific PCR is of great diagnostic value. The *cps1F, cps1G* and *cps1I* probes hybridized with serotype 1 as well as with serotype 14 strains. In coagglutination tests, type 1 strains react with the anti-type 1 as well as with the anti-type 14 antisera (56). This suggests the presence of common epitopes between these serotypes. On the other hand, type 1 strains agglutinated only with anti-type 1 serum (56, 57), indicating that it is possible to detect differences between those serotypes.

[0148] The *cps2F, cps2G, cps2H, cps2I* and *cps2J* probes hybridized with serotypes 2 and 1/2 only. Serotype 34 showed a weak hybridizing signal with the *cps2G* probe. As shown in agglutination tests, type 1/2 strains react with sera directed against type 1 as well as with sera directed against type 2 strains (46). Therefore, type 1/2 shared antigens with both types 1 and 2. Based on the hybridization patterns of serotype 1/2 strains with the *cps1* and *cps2* specific genes, serotype 1/2 seemed to be more closely related to type 2 strains than to type 1 strains. In our current studies, we identify type-specific genes, primers or probes which are used for the discrimination of serotypes 1, 14 and 2 and 1/2 and others of the 35 serotypes yet known. Furthermore, type-specific genes, primers or probes can now easily be developed for yet unknown serotypes, once they become isolated.

Cloning and characterization of a further part of the cps2 locus.

[0149] Based on the established sequence, 11 genes, designated cps2L to cps2T, orf2U and orf2V, were identified. A gene homologous to genes involved in the polymerization of the repeating oligosaccharide unit (cps2O) as well as genes involved in the synthesis of sialic acid (cps2P to cps2T) were identified. Moreover, hybridization experiments showed that the genes involved in the sialic acid synthesis are present in *S. suis* serotypes 1, 2, 14, 27 and 1/2. The "cps2M" and "cps2N" regions showed similarity to proteins involved in the polysaccharide biosynthesis of other [g]Gram-positive bacteria. However, these regions seemed to be truncated

or were nonfunctional as the result of frame-shift or point mutations. At its 3' -end, the cps2 locus contained two insertional elements ("orf2U" and "orf2V"), both of which seemed to be non-functional.

[0150] To clone the remaining part of the cps2 locus, sequences of the 3'-end of pCPS26 (FIG. 1, part C) were used to identify a chromosomal fragment containing cps2 sequences located further downstream. This fragment was cloned in pKUN19, resulting in pCPS29. Using a similar approach, we subsequently isolated the plasmids pCPS30 and pCPS34 containing downstream cps2 sequences (FIG. 1, part C).

Analysis of the cps2 operon.

[0151] The complete nucleotide sequence of the cloned fragments was determined. Examination of the compiled sequence revealed the presence of:[ ] a sequence encoding the C-terminal part of Cps2K, six apparently functional genes (designated cps2O-cps2T) and the remnants of 5 different ancestral genes (designated "cps2L", "cps2M", "cps2N", "orf2U" and "orf2V"). The latter genes seemed to be truncated or incomplete as the result of the presence of stop codons or frame-shift mutations [Fig. 1A] (FIG. 1, part A). Neither potential promoter sequences nor potential stem-loop structures could be identified within the sequenced region. A ribosome-binding site precedes each ORF and the majority of the ORFs are very closely linked. Three intergenic gaps were found: one between "cps2M" and "cps2N" (176 nucleotides), one between cps2O and cps2P (525 nucleotides), and one between cps2T and "orf2U" (200 nucleotides). These and our above data show that Orf2X and Cps2A-Orf2T are part of a single operon.

[0152] A list of all loci and their properties is shown in Table 4. The "cps2L" region contained three potential ORFs[,] of 103, 79 and 152 amino acids, respectively, which were only separated from each other by stop codons. Only the first ORF is preceded by a potential ribosomal binding site and contained a methionine start codon. This suggests that "cps2L" originates from an ancestral cps2L gene, which coded for a protein of 339 amino acids. The function of this hypothetical Cps2L protein remains unclear so far: no significant homologies were found between Cps2L and proteins present in the data libraries. It is not clear whether the first ORF of the

"cps2L" region is expressed into a protein of 103 amino acids. The "cps2M" region showed homology to the N-terminal 134 amino acids of the NeuA proteins of *Streptococcus agalactiae* and *Escherichia coli* (AB017355, 32). However, although the "cps2 M" region contained a potential ribosome binding site, a methionine start codon was absent. Compared with the *S. agalactiae* sequence, the ATG start codon was replaced by a lysin encoding AAG codon. Moreover, the region homologous to the first 58 amino acids of the *S. agalactiae* NeuA (identity 77%) was separated from the region homologous to amino acids 59-134 of NeuA by a repeated DNA sequence of 100-bp (*see*, herein). In addition, the region homologous to amino acids 59 to 95 of NeuA (identity 32%) and the region homologous to the amino acids 96 to 134 of NeuA (identity 50%) were present in different reading frames. Therefore, the partial and truncated NeuA homologue is probably nonfunctional in *S. suis*. The "cps2N" region showed homology to CpsJ of *S. agalactiae* (accession no. AB017355). However, sequences homologous to the first 88 amino acids of CpsJ were lacking in *S. suis*. Moreover, the homologous region was present in two different reading frames. The protein encoded by the cps2O gene showed homology to proteins of several streptococci involved in the transport of the oligosaccharide repeating unit (accession no. AB017355), suggesting a similar function for Cps2O. The proteins encoded by the cps2P, cps2S and cps2T genes showed homology to the NeuB, NeuD and NeuA proteins of *S. agalactiae* and *E. coli* (accession no. AB017355). Because the "cps2M" region also showed homology to NeuA of *E. coli*, the *S. suis* cps2 locus contains a functional neuA gene (cps2T) as well as a nonfunctional ("cps2M") gene. The mutual homology between these two regions showed an identity of 77% at the amino acid level over amino acids 1-58 and 49% over the amino acids 59-134. Cps2Q and Cps2R showed homology to the N-terminal and C-terminal parts of the NeuC protein of *S. agalactiae* and *E. coli*, respectively. This suggests that the function of the *S. agalactiae* NeuC protein in *S. suis* is likely fulfilled by two different proteins. In *E. coli*, the neu genes are known to be involved in the synthesis of sialic acid. NeuNAc is synthesized from N-acetylmannosamine and phosphoenolpyruvate by NeuNAc synthetase. Subsequently, NeuNAc is converted to CMP-NeuNAc by the enzyme CMP-NeuNAc synthetase. CMP-NeuNAc is the substrate for the synthesis of polysaccharide. In *E. coli*, K1 NeuB is the NeuNAc synthetase, and NeuA is the CMP-NeuNAc synthetase. NeuC has been implicated in the NeuNAc synthesis, but

its precise role is not known. The precise role of NeuD is not known. A role of the Cps2P-Cps2T proteins in the synthesis of sialic acid can easily be envisaged, since the capsule of *S. suis* serotype 2 is rich in sialic acid. In *S. agalactiae*, sialic acid has been shown to be critical to the virulence function of the type III capsule. Moreover, it has been suggested that the presence of sialic acid in the capsule of bacteria which can cause meningitis may be important for these bacteria to breach the blood-brain barrier. So far, however, the requirement of the sialic acid for virulence of *S. suis* remains unclear.

[0153] "Orf2U" and "Orf2V" showed homology to proteins located on two different insertional elements. "Orf2U" is homologous to IS1194 of *Streptococcus thermophilus*, whereas "Orf2V" showed homology to a putative transposase of *Streptococcus pneumoniae*. This putative transposase was recently found to be associated with the type 2 capsular locus of *S. pneunioniae*. Compared with the original insertional elements in *S. thermophilus* and *S. pneumoniae*, both "Orf2U" and "Orf2V" are likely to be non[-]functional due to frame shift mutations within their coding regions.

[0154] A striking observation was the presence of a sequence of 100 bp (FIG. 10) which was repeated three times within the cps2 operon. The sequence is highly conserved (between 94% and 98%) and was found in the intergenic regions between cps2G and cps2H, within "cps2M" and between cps2O and cps2P. No significant homologies were found between this 100-bp direct repeat sequence and sequences present in the data libraries, suggesting that the sequence is unique for *S. suis*.

Distribution of the cps2 sequences among the 35 *S. suis* serotypes.

[0155] To examine the presence of sialic acid encoding genes in other *S. suis* serotypes, we performed cross-hybridization experiments. DNA fragments of the individual cps2 genes were amplified by PCR, radiolabeled with 32P and hybridized to chromosomal DNA of the reference strains of the 35 different *S. suis* serotypes. As a positive control, we used a probe specific for *S. suis* 16S rRNA. The 16S rRNA probe hybridized with almost equal intensities to all serotypes tested (Table 4). The "cps2L" sequence hybridized with DNA of serotypes 1, 2, 14 and 1/2. The "cps2M", cps2O, cps2P, cps2Q, cps2R, cps2S and cps2T genes hybridized with DNA of serotypes

1, 2, 14, 27 and 1/2. Because the cps2P-cps2T genes are most likely involved in the synthesis of sialic acid, these results suggest that sialic acid is also a part of the capsule in the *S. suis* serotypes 1, 2, 14, 27 and 1/2. This is in agreement with the finding that the serotypes 1, 2 and 1/2 possess a capsule that is rich in sialic acid. Although the chemical compositions of the capsules of serotypes 14 and 27 are unknown, recent agglutination studies using sialic acid-binding lectins suggested the presence of sialic acid in *S. suis* serotype 14, but not in serotype 27. In these studies, sialic acid was also detected in serotypes 15 and 16. Since the latter observation is not in agreement with our hybridization studies, it might be that other genes, not homologous to the cps2P-cps2T genes, are responsible for the sialic acid synthesis in serotypes 15 and 16.

[0156] A probe based on "cps2N" sequences hybridized with DNA from serotypes 1, 2, 14 and 1/2. A probe specific for "orf2U" hybridized with serotypes 1, 2, 7, 14, 24, 27, 32, 34, and 1/2, whereas a probe specific for 'orf2V" hybridized with many different serotypes. In addition, we prepared a probe specific for the 100-bp direct repeat sequence. This probe hybridized with the serotypes 1, 2, 13, 14, 22, 24, 27, 29, 32, 34 and 1/2 (Table 4). To analyze the number of copies of the direct repeat sequence within the *S. suis* serotype 2 chromosome, a Southern blot hybridization and analysis was performed. Therefore, chromosomal DNA of *S. suis* serotype 2 was digested with NcoI and hybridized with a 32P-labeled direct repeat sequence. Only one hybridizing fragment, containing the three direct repeats present on the cps2 locus, was found (results not shown). This indicates that the 100-bp direct repeat sequence is only associated with the cps2 locus. In *S. pneumoniae*, a 115-bp long repeated sequence was found to be associated with the capsular genes of serotypes 1, 3, 14 and 19F. In *S. pneumoniae*, this 115-bp sequence was also found in the vicinity of other genes involved in pneumococcal virulence (hyaluronidase and neuraminidase genes). A regulatory role of the 115-bp sequence in co[-]ordinate control of these virulence- related genes was suggested.

[0157] To study the role of the capsule in resistance to phagocytosis and in virulence, we constructed two isogenic mutants in which capsule synthesis was disturbed. In 10cpsB, the *cps2B* gene was disturbed by the insertion of an antibiotic-resistance gene, whereas in 10cpsEF, parts of the *cps2E* and *cps2F* genes were replaced. Both mutant strains seemed to be completely unencapsulated. Because the [*cps 2*]*cps2* genes seemed to be part of an operon, polar effects

cannot be excluded. Therefore, these data did not give any information about the role of Cps2B, Cps2E or Cps2F in the polysaccharide biosynthesis. However, the results clearly show that the capsular polysaccharide of *S. suis* type 2 is a surface component with antiphagocytic activity. *In vitro* wild type encapsulated bacteria are ingested by phagocytes at a very low frequency, whereas the mutant unencapsulated bacteria are efficiently ingested by porcine macrophages. Within 2 hours, over 99.6% of mutant bacteria were ingested and over 92% of the ingested bacteria were killed. Intracellularly, wild type as well as mutant strains seemed to be killed with the same efficiency. This suggests that the loss of capsular material is associated with loss of capacity to resist uptake by macrophages. This loss of resistance to *in vitro* phagocytosis was associated with a substantial attenuation of the virulence in germfree pigs. All pigs inoculated with the mutant strains survived the experiment and did not show any specific clinical signs of disease. Only some aspecific clinical signs of disease could be observed. Moreover, mutant bacteria could be reisolated from the pigs. This supports the idea that, as in other pathogenic Streptococci, the capsule of *S. suis* acts as an important virulence factor. Transposon mutants prepared by Charland impaired in the capsule production showed a reduced virulence in pigs and mice. To construct these mutants, the type 2 reference strain S735 was used. We previously showed that this strain is only weakly virulent for young pigs. Moreover, the insertion site of the transposon is unsolved so far.

As a further example herein, a rapid PCT test for *Streptococcus suis type* 7 is described.

[0158] Recent epidemiological studies on *Streptococcus suis* infections in pigs indicated that, besides serotypes 1, 2 and 9, serotype 7 is also frequently associated with diseased animals. For the latter serotype, however, no rapid and sensitive diagnostic methods are available. This hampers prevention and control programs. Here we describe the development of a type-specific PCR test for the rapid and sensitive detection of *S. suis* serotype 7. The test is based on DNA sequences of capsular (cps) genes specific for serotype 7. These sequences could be identified by cross-hybridization of several individual cps genes with the chromosomal DNAs of 35 different *S. suis* serotypes.

[0159] *Streptococcus suis* is an important cause of meningitis, septicemia, arthritis and sudden death in young pigs (69, 70). It can, however, also cause meningitis in man (71). Attempts to control the disease are still hampered by the lack of sufficient knowledge about the epidemiology of the disease and the lack of effective vaccines and sensitive diagnostics.

[0160] *S. suis* strains can be identified and classified by their morphological, biochemical and serological characteristics (70, 73, 74). Serological classification is based on the presence of specific antigenic determinants. Isolated and biochemically characterized *S. suis* cells are agglutinated with a panel of specific sera. These typing methods are very laborious and time-consuming and can only be performed on isolated colonies. Moreover, it has been reported that nonspecific cross-reactions may occur among different types of *S. suis* (75, 76).

[0161] So far, 35 different serotypes have been described (7, 78, 79). *S. suis* serotype 2 is the most prevalent type isolated from diseased pigs, followed by serotypes 9[,] and 1. However, recently, serotype 7 strains were also frequently isolated from diseased pigs (80, 81, 82). This suggests that infections with *S. suis* serotype 7 strains seem to be an increasing problem. Moreover, the virulence of *S. suis* serotype 7 strains was confirmed by experimental infection of young pigs (83).

[0162] Recently, rapid and sensitive PCR assays specific for serotypes 2 (and 1/2), 1 (and 14) and 9 were developed (84). These assays were based on the cps loci of *S. suis* serotypes 2, 1 and 9 (84, 85). However, until now, no rapid and sensitive diagnostic test [is]was available for *S. suis* serotype 7. Herein we describe the development of a PCR test for the rapid and sensitive detection of *S. suis* serotype 7 strains. The test is based on DNA sequences which form a part of the cps locus of *S. suis* serotype 7. Compared with the serological serotyping methods, the PCR assay was a rapid, reliable and sensitive assay. Therefore, this test, in combination with the PCR tests which we previously developed for serotypes 1, 2 and 9, will undoubtedly contribute to a more rapid and reliable diagnosis of *S. suis* and may facilitate control and eradication programs.

Materials and Methods

Bacterial strains, growth conditions and serotyping.

[0163] The bacterial strains and plasmids used in this study are listed in Table 7. The *S. suis* reference strains were obtained from M. Gottschalk, Canada. *S. suis* strains were grown in Todd-Hewitt broth (code CM189, Oxoid), and plated on Columbia agar blood base (code CM331, Oxoid) containing 6% (v/v) horse blood. *E. coli* strains were grown in Luria broth (86) and plated on Luria broth containing 1.5% (w/v) agar. If required, ampicillin was added to the plates. The *S. suis* strains were serotyped by the slide agglutination test with serotype-specific antibodies (70).

DNA techniques.

[0164] Routine DNA manipulations and PCR reactions were performed as described by Sambrook et al. (88). Blotting and hybridization [was]were performed as described previously (84, 86).

DNA sequence analysis.

[0165] DNA sequences were determined on a 373A DNA Sequencing System (Applied Biosystems, Warrington, GB). Samples were prepared by use of an ABI/PRISM dye terminator cycle sequencing ready reaction kit (Applied Biosystems). Custom-made sequencing primers were purchased from Life Technologies. Sequencing data were assembled and analyzed using the McMollyTetra program. The BLAST program was used to search for protein sequences homologous to the deduced amino acid sequences.

PCR.

[0166] The primers used for the cps7H PCR correspond to the positions 3334-3354 and 3585-3565 in the *S. suis* cps7 locus.

The sequences were:

5' -AGCTCTAACACGAAATAAGGC-3' (SEQ. ID. No. 7) and

5' -GTCAAACACCCTGGATAGCCG3' (SEQ. ID. No. 8).

The reaction mixtures contained 10 mM Tris-HC1, pH 8.3; 1.5 mM

MgC12; 50 mM KC1; 0.2 mM of each of the four deoxynucleotide triphosphates; 1 microM of each of the primers and 1U of AmpliTaq Gold DNA polymerase (Perkin Elmer Applied Biosystems, New Jersey). DNA amplification was carried out in a Perkin Elmer 9600 thermal cycler and the program consisted of an incubation for 10 min at 95°C and 30 cycles of 1 min at 95°C, 2 min at 56°C and 2 min at 72°C.

Results and discussion

Cloning of the seroytpe 7-specific cps genes.

[0167] To isolate the type-specific cps genes of *S. suis* serotype 7, we used the cps9E gene of serotype 9 as a probe to identify chromosomal DNA fragments of type 7 containing homologous DNA sequences (84). A 1.6-kb PstI fragment was identified and cloned in pKUN19. This yielded pCPS7-1 (FIG. 11, part C). In turn, this fragment was used as a probe to identify an overlapping 2.7 kb ScaI-ClaI fragment. pGEM7 containing the latter fragment was designated pCPS7-2 (FIG. 11, part C).

Analysis of the cloned cps7 genes.

[0168] The complete nucleotide sequences of the inserts of pCPS7-1, pCPS7-2 were determined. Examination of the cps7 sequence revealed the presence of two complete and two incomplete open reading frames (ORFs) (FIG. 11, part C). All ORFs are preceded by a ribosome-binding Site. In accord with the data obtained for the cps1, cps2 and cps9 genes of serotypes 1, 2 and 9, respectively, the type 7 ORFs are very closely linked to each other. The only significant intergenic gap was that found between cps7E and cps7F (443 nucleotides). No obvious promoter sequences or potential stem-loop structures were found in this region. This suggests that, as in serotypes 1, 2 and 9, the cps genes in serotype 7 form part of an operon.

[0169] An overview of the ORFs and their properties is shown in Table 8. As expected on the basis of the hybridization data (84), the Cps9E and Cps7E proteins showed a high similarity (identity 99%, Table 8). Based on sequence comparisons between Cps9E and Cps7E, the PstI fragment of pCPS7-1 lacks the region encoding the first 371 codons of Cps7E. The C-terminal part of the protein encoded by the cps7F gene showed some similarity with the Bp1G protein of

Bordetella pertussis (88), as well as with the C-terminal part of *S. suis* Cps2E (85). Both Bp1G and Cps2E were suggested to have glycosyltransferase activity and are probably involved in the linkage of the first sugar to the lipid carrier (85, 88). The protein encoded by the cps7G gene showed similarity with the [B1pF] Bp1F protein of *Bordetella pertussis* (88). Bp1F is likely to be involved in the biosynthesis of an amino sugar, suggesting a similar function for Cps7G. The protein encoded by the cps7H gene showed similarity with the WbdN protein of *E. coli* (89) as well as with the N-terminal part of the Cps2K protein of *S. suis* (81). Both WbdN and Cps2K were suggested to have glycosyltransferase activity (85, 89).

Serotype 7 specific cps genes.

[0170] To determine whether the cloned fragments in pCPS7-1 and pCPS7-2 contained serotype 7-specific DNA sequences, cross[ ]-hybridization experiments were performed. DNA fragments of the individual cps7 genes were amplified by PCR, labeled with 32P, and used to probe spot blots of chromosomal DNA of the reference strains of 35 different *S. suis* serotypes. The results are summarized in Table 9. As expected, based on the data obtained with the cps9E probe (84), the cps7E probe hybridized with chromosomal DNA of many different *S. suis* serotypes. The cps7F and cps7G probes showed hybridization with chromosomal DNA of *S. suis* serotypes 4, 5, 7, 17, and 23. However, the cps7H probe hybridized with chromosomal DNA of serotype 7 only, indicating that this gene is specific for serotype 7.

Type specific PCR.

[0171] We tested whether we could use PCR instead of hybridization for the typing of the *S. suis* serotype 7 strains. For that purpose, we selected an oligonucleotide primer set within the cps7H gene with which an amplified fragment of 251-bp was expected. In addition, we included in our analysis several *S. suis* serotype 7 strains, other than the reference strain. These strains were obtained from different countries and were isolated from different organs (Table 7). The results show that indeed a fragment of about 250-bp was amplified with all type 7 strains used (FIG. 12, part B), whereas no PCR products were obtained with serotype 1, 2 and 9 strains (FIG. 12, part A). This suggests that the PCR test, as described here, is a rapid diagnostic tool for

the identification of *S. suis* serotype 7 strains. Until now, such a diagnostic test was not available for serotype 7 Strains. Together with the recently developed PCR assays for serotypes 1, 2, 1/2, 14 and 9, this assay may be an important diagnostic tool to detect pigs carrying serotype 2, 1/2, 1, 14, 9 and 7 strains and may facilitate control and eradication programs.

TABLE 1. Bacterial strains and plasmids

strain/plasmid	relevant characteristics	source/reference
Strain		
E.coli		
CC118	PhoA$^-$	(28)
XL2 blue	Stratagene	
E.coli		
XL2 blue	Stratagene	
S. suis		
10	virulent serotype 2 strain	(49)
3	serotype 2	(63)
17	serotype 2	(63)
735	reference strain serotype 2	(63)
T15	serotype 2	(63)
6555	reference strain serotype 1	(63)
6388	serotype 1	(63)
6290	serotype 1	(63)
5637	serotype 1	(63)
5673	serotype 1/2	(63)
5679	serotype 1/2	(63)
5928	serotype 1/2	(63)
5934	serotype 1/2	(63)
5209	reference strains serotype 1/2	(63)
5218	reference strain serotype 9	(63)
5973	serotype 9	(63)
6437	serotype 9	(63)
6207	serotype 9	(63)
reference strains	serotypes 1-34	(9, 56, 14)
S. suis		
10	virulent serotype 2 strain	(51)
10cpsB	isogenic cpsB mutant of strain 10	this work
10cpsEF	isogenic cpsEF mutant of strain 10	this work
Plasmid		
pKUN19	replication functions pUC, Amp^R	(23)
pGEM7Zf(+)	replication functions pUC, Amp^R	Promega Corp.
pIC19R	replication functions pUC, Amp^R	(29)
pIC20R	replication functions pUC, Amp^R	(29)
pIC-spc	pIC19R containing spc^R gene of pDL282	labcollection

pDL282	replication functions of pBR322 a pVT736-1, Amp^R, Spc^R	(43)
pPHOS2	pIC-spc containing the truncated *pho*A gene of pPHO7 as a *Pst*I-*Bam*HI fragment	this work
pPHO7	contains truncated *pho*A gene	(15)
pPHOS7	pPHOS2 containing chromosomal *S. suis* DNA	this work
pCPS6	pKUN19 containing 6 kb *Hin*dIII fragment of *cps* operon	this work (Fig.1)
pCPS7	pKUN19 containing 3,5 kb *Eco*RI-*Hin*dIII fragment of *cps* operon	this work (Fig.1)
pCPS11	pCPS7 in which 0.4 kb *Pst*I-*Bam*HI fragment of *cps*B gene is replaced by Spc^R gene of pIC-spc	this work (Fig.1)
pCPS17	pKUN19 containing 3.1 kb *Kpn*I fragment of *cps* operon	this work (Fig.1)
pCPS18	pKUN19 containing 1.8 kb *Sna*BI fragment of *cps* operon	this work (Fig.1)
pCPS20	pKUN19 containing 3.3 kb *Xba*I-*Hin*dIII fragment of *cps* operon	this work (Fig.1)
pCPS23	pGEM7Zf(+) containing 1.5 kb *Mlu*I fragment of *cps* operon	this work (Fig.1)
pCPS25	pIC20R containing 2.5 kb *Kpn*I-*Sal*I fragment of pCPS17	this work (Fig.1)
pCPS26	pKUN19 containing 3.0 kb *Hin*dIII fragment of *cps* operon	this work (Fig.1)
pCPS27	pCPS25 containing 2.3 kb *Xba*I (blunt)-*Cla*I fragment of pCPS20	this work (Fig.1)
pCPS28	pCPS27 containing the 1.2 kb *Pst*I-*Xho*I Spc^R gene of pIC-spc	this work (Fig.1)
pCPS29	pKUN19 containing 2.2 kb *Sac*I-*Pst*I fragment of cps operon	this work (Fig.1)
pCPS1-1	pKUN19 containing 5 kb *Eco*RV fragment of *cps* operon of type 1	this work (Fig.1)
pCPS1-2	pKUN19 containing 2.2 kb *Hin*dIII fragment of *cps* operon of type 1	this work (Fig.1)
pCPS9-1	pKUN19 containing 1 kb *Hin*dIII-*Xba*I fragment of *cps* operon of serotype 9	this work (Fig.1)
pCPS9-2	pKUN19 containing 4.0 kb *Xba*I-*Xba*I fragment of *cps* operon of serotype 9	this work (Fig.1)

Amp^R: ampicillin resistant
Spc^R: spectinomycin resistant
cps: capsular polysaccharide

Table 1 continued

Table 2. Properties of Orfs in the cps locus of S. suis serotype 2 and similarities to gene product other bacteria

ORF	nucleotide position in sequence	number of amino acids	GC%	proposed function of gene product[1]	similar gene product (% identity)
Orf2Z	1 -719	240	44	Unknown	*B. subtilis* YitS (26%)
Orf2Y	2079-822	419	38	Transcription regulation	*B. subtilis* YcxD (39%)
Orf2X	2202-2934	244	39	Unknown	*H. influenzae* YAAA (24%)
Cps2A	3041-4484	481	39	Regulation	*S. pneumoniae* Cps19fA (58%)
Cps2B	4504-5191	229	40	Chain length determination	*S. pneumoniae* type 3 Orf1 (58%)
Cps2C	5203-5878	225	40	Chain length determination/ Export	*S. pneumoniae* Cps23fD (63%)
Cps2D	5919-6648	243	38	Unknown	*S. pneumoniae* CpsB (62%)
Cps2E	6675-8052	459	33	Glycosyltransferase	*S. pneumoniae* Cps14E (56%)
Cps2F	8089-9256	389	32	Glycosyltransferase	*S. pneumoniae* Cps23fT
Cps2G	9262-10417	385	36	Glycosyltransferase	*S. thermophilus* EpsF (25%)
Cps2H	10808-12176	457	31	Glycosyltransferase	*S. mutans* RGPEC,[N] (29%)
Cps2I	12213- 13443	410	29	CP polymerase	*S. pneumoniae* Cps23fI (48%)
Cps2J	13583-14579	332	29	Glycosyltransferase	*S. pneumoniae* Cps14J (31%)
Cps2K	14574-15576	334	37	Glycosyltransferase	*S. pneumoniae* Cps14J (40%)

Table 2 continued

"Cps2L"	15618-16635	103	37	Unknown	-
"Cps2M"	16811-17322	-	38	-	*S. agalactiae* CpsF^{N} (77%)
					E. coli NeuA ^{,N} (47%)
"Cps2N"	17559-18342	-	39	-	*S. agalactiae* CpsJ (43%)
Cps2O	18401-19802	476	40	Repeat unit transporter	*S. agalactiae* CpsK (41%)
Cps2P	20327-21341	338	39	Sialic acid synthesis	*S. agalactiae* NeuB (80%) *E. coli* NeuB (59%)
Cps2Q	21355-21865	170	42	Sialic acid synthesis	*S. agalactiae* NeuC^{N} (61%) *E. coli* NeuC^{N} (54%)
Cps2R	21933-22483	184	40	Sialic acid synthesis	*S. agalactiae* NeuC^{C} (55%) *E. coli* NeuC^{C} (40%)
Cps2S	22501-23125	208	42	Sialic acid synthesis	*E. coli* NeuD (32%)
Cps2T	23136-24366	395	40	CMP-NeuNAc synthetase	*S. agalactiae* CpsF (49%) *E.coli* NeuA (34%)
"Orf2U"	24566-25488	168	42	Transposase	*S. thermophilus* IS1194 (51%)
"Orf2V"	25691-26281	116	37	Transposase	*S. pneumoniae* orf1 (85%)

[1]Predicted by sequence similarity
[N] Similarity refers to the amino-terminal part of the gene product
[C] Similarity refers to the carboxy-terminal part of the gene product
ORFs between " " are truncated or non-functional as the result of frame-shift or point mutations

Table 3. Properties of Orfs in the cps genes of S. suis serotypes 1 and 9 and similarities to gene products of other bacteria

ORF	nucleotide position in sequence	G + C%	number of amino acids	predicted mol. mass (kDa)	predicted pI	proposed function of gene product[1]	similar gene product (% identity)	reference accession nr.
Cps1E[2] (48%)	1-1363	34%	454	52.2	8.0	Glucosyltransferase	*Streptococcus suis* Cps2E (86%) *Streptococcus pneumoniae* Cps14E	(26) (12)
Cps1F	1374-1821	33%	149	17.3	8.2	Unknown	*Streptococcus pneumoniae* Cps14F (83%)	(14)
Cps1G	1823-2315	25%	164	19.5	7.5	Glycosyltransferase	*Streptococcus pneumoniae* Cps14G (50%)	(14)
Cps1H	3035-4202	24%	389	45.5	8.4	CP polymerase	*Streptococcus pneumoniae* Cps14H (30%)	(14)
Cps1I	4197-					Glycosyltransferase	*Streptococcus pneumoniae* Cps14J (38%) *Lactococcus lactis* EpsG (31%) *Streptococcus thermophilus* EpsI (33%)	(13) (29) (28)
Cps1J						Glycosyltransferase	*Streptococcus pneumoniae* Cps14J ( )	

Table 3 continued

							(13)
Cps1K[3]		37%	278	32.5	7.8	Glycosyltransferase	*Streptococcus pneumoniae* Cps14J (44%) (13)
Cps9D[2]	1-646	37%	215	24.9	8.1	Unknown	*Streptococcus suis* Cps2D (89%) (26)
Cps9E	680-					Glycosyltransferase	*Staphylococcus aureus* Cap1D (27%) (18)
Cps9F		36%	200	22.3	8.2	Glycosyltransferase	*Staphylococcus aureus* Cap5M (52%) (17)
Cps9G		35%	269	31.5	8.0	Unknown	*Actinobacillus actinomycetemcomitans* (43%) (AB002668_4) *Haemophilus influenzae* Lsg (43%) (O05081)
Cps9H[3]		30%	143	16.5	7.2	Unknown	*Yersinia enterolitica* RfbB (28%) (33)

[1]Predicted by sequence similarity

[2] N-terminal part of protein is lacking

[3] C-terminal part of protein is lacking

Table 4. **Hybridization of serotype 2 cps genes and neighboring sequences with chromosomal DNA of other serotypes**

serotypes	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	1/2
DNA probes																																			
orf2Z	+	+	+	+	+	+	+	+	+	+	+	+	±	+	+	+	+	+	+	-	+	-	+	+	+	-	+	+	+	+	+	-	-	-	+
orf2Y	+	+	+	+	+	+	+	+	+	+	+	+	±	+	+	+	+	+	+	±	+	±	+	+	+	+	+	+	+	+	+	-	-	-	+
orf2X	+	+	+	+	+	+	+	+	+	+	+	+	±	+	+	+	+	+	+	-	+	-	+	+	+	-	+	+	+	+	+	-	-	-	+
cps2A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	-	+	+	+	+	+	-	-	-	+
cps2B	+	+	+	+	+	+	+	+	+	+	-	-	±	+	-	-	±	±	±	-	±	-	+	+	+	-	+	+	+	±	+	-	±	-	+
cps2C	+	+	+	+	+	+	+	+	+	+	+	-	±	+	-	±	-	-	-	-	-	-	+	+	+	-	+	±	-	±	+	-	±	-	+
cps2D	+	+	-	-	-	-	-	-	-	-	±	±	+	-	±	+	+	+	-	±	-	+	+	+	-	+	±	-	+	+	-	-	-	+
cps2E	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
cps2F	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	+
cps2G	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
cps2H	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±	+
cps2I	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
cps2J	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
cps2K	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
"cps2L"	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
"cps2M"	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	+
"cps2N"	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
cps2O	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	+
cps2P	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+
cps2Q	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	+
cps2R	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	+
cps2S	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	+
cps2T	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	+
"orf2U"	+	+	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	+	-	+	+
"orf2V"	+	+	±	±	±	-	±	-	-	-	-	-	-	+	+	-	+	+	±	-	-	±	+	-	-	+	-	-	-	+	+	-	±	+
100-bp repeat	+	+	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	+	-	+	-	-	+	-	-	-	-	+	-	+	+
16SrRNA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table 5. Hybridization of serotypes 1 and 9 *cps* genes with chromosomal DNA of other *S. suis* serotypes

	DNA probes									
Serotype	*cps1E*	*cps1F*	*cps1G*	*cps1H*	*cps1I*	*cps9E*	*cps9F*	*cps9G*	*cps9H*	16rRNA
1	+	+	+	+	+	-	-	-	-	+
2	+	-	-	-	-	-	-	-	-	+
3	-	-	-	+	-	+	-	-	-	+
4	-	-	-	+	-	+	-	-	-	+
5	-	-	-	+	-	+	-	-	-	+
6	-	-	-	-	-	-	-	-	-	+
7	-	-	-	+	-	+	-	-	-	+
8	-	-	-	-	-	-	-	-	-	+
9	-	-	-	+	-	+	+	+	+	+
10	-	-	-	+	-	+	+	-	-	+
11	-	-	-	+	-	+	±	-	-	+
12	-	-	-	±	-	+	±	-	-	+
13	-	-	-	+	-	+	-	-	-	+
14	+	+	+	+	+	-	-	-	-	+
15	-	-	-	-	-	-	-	-	-	+
16	-	-	-	-	-	-	-	-	-	+
17	-	-	-	+	-	+	-	-	-	+
18	-	-	-	+	-	+	-	-	-	+
19	-	-	-	+	-	+	-	-	-	+
20	-	-	-	-	-	-	-	-	-	+
21	-	-	-	+	-	+	±	-	-	+
22	-	-	-	-	-	-	-	-	-	+

Table 5 continued

23	-	-	-	+	-	+	-	-	-	+
24	-	-	-	+	-	+	+	-	-	+
25	-	-	-	-	-	-	-	-	-	+
26	-	-	-	-	-	-	±	-	-	+
27	+	-	-	-	-	-	-	-	-	+
28	-	-	-	+	-	+	±	-	-	+
29	-	-	-	+	-	+	-	-	-	+
30	-	-	-	+	-	+	±	-	-	+
31	-	-	-	+	-	+	-	-	-	+
32	-	-	-	-	-	-	-	-	-	+
33	-	-	-	-	-	-	±	-	-	+
34	-	-	-	-	-	-	-	-	-	+
1/2	+	-	-	-	-	-	-	-	-	+

TABLE 6. Virulence of wild type and capsular mutant *S. suis* strains in germfree pigs

S. suis strains[1]	pigs/ group [n]	mortality[2] [%]	morbidity[3] [%]	clinical index of the group		fever index[7]	leuco-cyte index[8]	isolation of *S. suis* in pigs [n] per group in		
				spec symptoms[5]	non-spec. symptoms[6]			CNS	serosae	joints
10	4	100	100	11	88	43	44	2	3	4
10cpsB	4	0	0	0	10	1	3	1	3	2
10cpsEF	4	0	0	0	0	1	0	1	3	2

[1] strain10 in the wild type strain, strains 10cpsB and 10cpsEF are isogenic capsular mutant strains

[2] piglets which died spontaneously or had to be killed for animal welfare reasons

[3] only considering pigs with specific symptoms

[4] clinical index: % of observations which matched the described criteria

[5] specific symptoms: ataxia, lameness on at least one joint, stiffness

[6] non-specific symptoms: inappetance, depression

[7] % of observations in the experimental group with a body temperature > 40^0 C

[8] % of blood samples in the group in which number of granulocytes > 10^{10}/l

Table 7. **Bacterial strains and plasmids**

strain/plasmid	relevant characteristics
Strain	
E.coli	
XL2 blue	
S. suis	
reference strains	serotypes 1-34
5667	serotype 7, tonsil (1993)
7037	serotype 7, organs (1994)
7044	serotype 7, brains (1994)
7068	serotype 7 (1994)
7646	serotype 7 (1994)
7744	serotype 7, lungs (1996)
7759	serotype 7, joints (1996)
8169	serotype 7 (1997)
15913	serotype 7, meninges (1998)
Plasmid	
pKUN19	replication functions pUC, Amp^R
pGEM7Zf(+)	replication functions pUC, Amp^R
pCPS9-1	pKUN19 containing 1 kb *HindIII-XbaI* fragment of *cps* operon of serotype 9
pCPS9-2	pKUN19 containing 4.0 kb *XbaI-XbaI* fragment of *cps* operon of serotype 9
pCPS7-1	pKUN19 containing 1.6-kb *PstI* fragment of *cps* operon of type 7
pCPS7-2	pGEM7 containing 2.7-kb *ScaI-ClaI* fragment of *cps* operon of type 7

*Amp^R; ampicillin resistant
cps: capsular polysaccharide

Table 8. Properties of Orfs in the *cps* genes of *S. suis* serotype 7 and similarities to gene products of other bacteria

Orf	nucleotide position in sequence	proposed function of gene product	similar gene product (% identity)
Cps7E	1-719	Glycosyltransferase	*Streptococcus suis* Cps9E (99%)
Cps7F	1164-1863	Glycosyltransferase	*Bordetella pertussis* BplG[1] (43%) *Streptococcus suis* Cps2E[1] (33%)
Cps7G	1872-3086	Biosynthesis amino sugar	*Bordetella pertussis* BplF (48%)
Cps7H	3104-3737	Glycosyltransferase	*Escherichia coli* WbdN (35%) *Streptococcus suis* Cps2K[2] (31%)

[1]similarity refers to the C-terminal part of the gene product
[2]similarity refers to the N-terminal part of the gene product

Table 9. Hybridization of serotype 7 *cps* probes with chromosomal DNA of *S. suis* serotypes

serotypes	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	1/2
DNA probes																																			
cps7E	-	-	+	+	+	-	+	-	+	+	+	+	+	-	-	-	+	+	+	-	+	-	+	+	-	-	-	-	+	+	+	-	-	-	-
cps7F	-	-	-	+	+	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
cps7G	-	-	-	+	+	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
cps7H	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
16SrRNA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

SEQUENCE LISTING

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cattttgtt ggagaataat ttcgcacttt caagacgtgg tgccgtgtat ttcacattaa 300

taaacttcgt tttggtatac ctatttaacg taattattaa gcagtttaag gatagctttc 360

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gacgaaaacg ggtatacaaa gaaaaaaaga aatagtaatt ttcatgtctt aacgagagaa 4620

gagactgtaa aagaattttt gtcaggatct aatatagaaa ataatgtttg gtgcaagctt 4680

tattcacgag atattataaa agatataaaa ttccaaatta ataatagaag tattggtgag 4740

gatttgcttt ttaatttgga ggtcttgaac aatgtaacac gtgtagtagt tgatactaga 4800

gaatattatt ataattatgt cattcgtaac agttcgctta ttaatcagaa attctctata 4860

aataatattg atttagtcac aagattggag aattacccct ttaagttaaa aagagagttt 4920

agtcattatt ttgatgcaaa agttattaaa gagaaggtta aatgtttaaa caaaatgtat 4980

tcaacagatt gtttggataa tgagttcttg ccaatattag agtcttatcg aaaagaaata 5040

cgtagatatc catttattaa agcgaaaaga tatttatcaa gaaagcattt agttacgttg 5100

tatttgatga aattttcgcc taaactatat gtaatgttat ataagaaatt tcaaaagcag 5160

tagaggtaaa aatggataaa attagtgtta ttgttccagt ttataatgta gataaatatt 5220

taagtagttg tatagaaagc attattaatc aaaattataa aaatatagaa atattattga 5280

tagatgatgg ctctgtagat gattctgcta aaatatgcaa ggaatatgca gaaaaagata 5340

aaagagtaaa aatttttttc actaatcata gtggagtatc aaatgctaga aatcatggaa 5400

taaagcggag tacagctgaa tatattatgt ttgttgactc tgatgatgtt gttgatagta 5460

gattagtaga aaaattatat tttaatatta taaaaagtag aagtgattta tctggttgtt 5520

tgtacgctac tttttcagaa aatataaata attttgaagt gaataatcca aatattgatt 5580

ttgaagcaat taataccgtg caggacatgg gagaaaaaaa ttttatgaat ttgtatataa 5640

ataatatttt ttctactcct gtttgtaaac tatataagaa aagatacata acagatcttt 5700

ttcaagagaa tcaatggtta ggagaagatt tacttttaa tctgcattat ttaaagaata 5760

tagatagagt tagttatttg actgaacatc tttatttta taggagaggt atactaagta 5820

cagtaaattc ttttaaagaa ggtgtgtttt tgcaattgga aaatttgcaa aaacaagtga 5880

tagtattgtt taagcaaata tatggtgagg attttgacgt atcaattgtt aaagatacta 5940

tacgttggca agtattttat tatagcttac taatgtttaa atacggaaaa cagtctattt 6000

ttgacaaatt tttaattttt agaaatcttt ataaaaaata ttattttaac ttgttaaaag 6060

tatctaacaa aaattctttg tctaaaaatt tttgtataag aattgtttcg aacaaagttt 6120

ttaaaaaaat attatggtta taataggaag atatcatgga tactattagt aaaatttcta 6180

taattgtacc tatatataat gtagaaaaat atttatctaa atgtatagat agcattgtaa 6240

atcagaccta caaacatata gagattcttc tggtgaatga cggtagtacg gataattcgg 6300

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acggcgggct atcagatgcc cgtaattatg gcataagtcg cgccaagggt gactacttag 6420

cttttataga ctcagatgat tttattcatt cggagttcat ccaacgttta cacgaagcaa 6480

ttgagagaga gaatgccctt gtggcagttg ctggttatga tagggtagat gcttcggggc 6540

atttcttaac agcagagccg cttcctacaa atcaggctgt tctgagcggc aggaatgttt 6600

gtaaaaagct gctagaggcg gatggtcatc gctttgtggt ggcctgtaat aaactctata 6660

aaaaagaact atttgaagat tttcgatttg aaaagggtaa gattcatgaa gatgaatact 6720

tcacttatcg cttgctctat gagttagaaa aagttgcaat agttaaggag tgcttgtact 6780

attatgttga ccgagaaaat agtatcacaa cttctagcat gactgaccat cgcttccatt 6840

gcctactgga atttcaaaat gaacgaatgg acttctatga aagtagagga gataaagagc 6900

tcttactaga gtgttatcgt tcatttttag cctttgctgt tttgttttta ggcaaatata 6960

atcattggtt gagcaaacag caaaagaagc tt 6992

<210> 10

<211> 239

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> ORF2Z

<400> 10

Ser Leu Asp Ile Asp His Met Met Glu Val Met Glu Ala Ser Lys Ser
1 5 10 15

Ala Ala Gly Ser Ala Cys Pro Ser Pro Gln Ala Tyr Gln Ala Ala Phe
20 25 30

Glu Gly Ala Glu Asn Ile Ile Val Val Thr Ile Thr Gly Gly Leu Ser
35 40 45

Gly Ser Phe Asn Ala Ala Arg Val Ala Arg Asp Met Tyr Ile Glu Glu
50 55 60

His Pro Asn Val Asn Ile His Leu Ile Asp Ser Leu Ser Ala Ser Gly
65 70 75 80

Glu Met Asp Leu Leu Val His Gln Ile Asn Arg Leu Ile Ser Ala Gly
85 90 95

Leu Asp Phe Pro Gln Val Val Glu Ala Ile Thr His Tyr Arg Glu His
100 105 110

Ser Lys Leu Leu Phe Val Leu Ala Lys Val Asp Asn Leu Val Lys Asn
115 120 125

Gly Arg Leu Ser Lys Leu Val Gly Thr Val Val Gly Leu Leu Asn Ile
130 135 140

Arg Met Val Gly Glu Ala Ser Ala Glu Gly Lys Leu Glu Leu Leu Gln
145 150 155 160

Lys Ala Arg Gly His Lys Lys Ser Val Thr Ala Ala Phe Glu Glu Met
165 170 175

Lys Lys Ala Gly Tyr Asp Gly Gly Arg Ile Val Met Ala His Arg Asn
180 185 190

Asn Ala Lys Phe Phe Gln Gln Phe Ser Glu Leu Val Lys Ala Ser Phe
195 200 205

Pro Thr Ala Val Ile Asp Glu Val Ala Thr Ser Gly Leu Cys Ser Phe
210 215 220

Tyr Ala Glu Glu Gly Gly Leu Leu Met Gly Tyr Glu Val Lys Ala
225 230 235

<210> 11

<211> 244

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> ORF2X

<400> 11

Met Lys Ile Ile Ile Pro Asn Ala Lys Glu Val Asn Thr Asn Leu Glu
1 5 10 15

Asn Ala Ser Phe Tyr Leu Leu Ser Asp Arg Ser Lys Pro Val Leu Asp
20 25 30

Ala Ile Ser Gln Phe Asp Val Lys Lys Met Ala Ala Phe Tyr Lys Leu
35 40 45

Asn Glu Ala Lys Ala Glu Leu Glu Ala Asp Arg Trp Tyr Arg Ile Arg
50 55 60

Thr Gly Gln Ala Lys Thr Tyr Pro Ala Trp Gln Leu Tyr Asp Gly Leu
65 70 75 80

Met Tyr Arg Tyr Met Asp Arg Arg Gly Ile Asp Ser Lys Glu Glu Asn
85 90 95

Tyr Leu Arg Asp His Val Arg Val Ala Thr Ala Leu Tyr Gly Leu Ile
100 105 110

His Pro Phe Glu Phe Ile Ser Pro His Arg Leu Asp Phe Gln Gly Ser
115 120 125

Leu Lys Ile Gly Asn Gln Ser Leu Lys Gln Tyr Trp Arg Pro Tyr Tyr
130 135 140

Asp Gln Glu Val Gly Asp Asp Glu Leu Ile Leu Ser Leu Ala Ser Ser
145 150 155 160

Glu Phe Glu Gln Val Phe Ser Pro Gln Ile Gln Lys Arg Leu Val Lys
165 170 175

Ile Leu Phe Met Glu Glu Lys Ala Gly Gln Leu Lys Val His Ser Thr
180 185 190

Ile Ser Lys Lys Gly Arg Gly Arg Leu Leu Ser Trp Leu Ala Lys Asn
195 200 205

Asn Ile Gln Glu Leu Ser Asp Ile Gln Asp Phe Lys Val Asp Gly Phe
210 215 220

Glu Tyr Cys Thr Ser Glu Ser Thr Ala Asn Gln Leu Thr Phe Ile Arg
225 230 235 240

Ser Ile Lys Met

<210> 12

<211> 481

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2A

<400> 12

Met Lys Lys Arg Ser Gly Arg Ser Lys Ser Ser Lys Phe Lys Leu Val
1 5 10 15

Asn Phe Ala Leu Leu Gly Leu Tyr Ser Ile Thr Leu Cys Leu Phe Leu
20 25 30

Val Thr Met Tyr Arg Tyr Asn Ile Leu Asp Phe Arg Tyr Leu Asn Tyr
35 40 45

Ile Val Thr Leu Leu Leu Val Gly Val Ala Val Leu Ala Gly Leu Leu
50 55 60

Met Trp Arg Lys Lys Ala Arg Ile Phe Thr Ala Leu Leu Leu Val Phe
65 70 75 80

Ser Leu Val Ile Thr Ser Val Gly Ile Tyr Gly Met Gln Glu Val Val
85 90 95

Lys Phe Ser Thr Arg Leu Asn Ser Asn Ser Thr Phe Ser Glu Tyr Glu
100 105 110

Met Ser Ile Leu Val Pro Ala Asn Ser Asp Ile Thr Asp Val Arg Gln
115 120 125

Leu Thr Ser Ile Leu Ala Pro Ala Glu Tyr Asp Gln Asp Asn Ile Thr
130 135 140

Ala Leu Leu Asp Asp Ile Ser Lys Met Glu Ser Thr Gln Leu Ala Thr
145 150 155 160

Ser Pro Gly Thr Ser Tyr Leu Thr Ala Tyr Gln Ser Met Leu Asn Gly
165 170 175

Glu Ser Gln Ala Met Val Phe Asn Gly Val Phe Thr Asn Ile Leu Glu
180 185 190

Asn Glu Asp Pro Gly Phe Ser Ser Lys Val Lys Lys Ile Tyr Ser Phe
195 200 205

Lys Val Thr Gln Thr Val Glu Thr Ala Thr Lys Gln Val Ser Gly Asp
210 215 220

Ser Phe Asn Ile Tyr Ile Ser Gly Ile Asp Ala Tyr Gly Pro Ile Ser
225 230 235 240

Thr Val Ser Arg Ser Asp Val Asn Ile Ile Met Thr Val Asn Arg Ala
245 250 255

Thr His Lys Ile Leu Leu Thr Thr Thr Pro Arg Asp Ser Tyr Val Ala
260 265 270

Phe Ala Asp Gly Gly Gln Asn Gln Tyr Asp Lys Leu Thr His Ala Gly
275 280 285

Ile Tyr Gly Val Asn Ala Ser Val His Thr Leu Glu Asn Phe Tyr Gly
290 295 300

Ile Asp Ile Ser Asn Tyr Val Arg Leu Asn Phe Ile Ser Phe Leu Gln
305 310 315 320

Leu Ile Asp Leu Val Gly Gly Ile Asp Val Tyr Asn Asp Gln Glu Phe
325 330 335

Thr Ser Leu His Gly Asn Tyr His Phe Pro Val Gly Gln Val His Leu
340 345 350

Asn Ser Asp Gln Ala Leu Gly Phe Val Arg Glu Arg Tyr Ser Leu Thr
355 360 365

Gly Gly Asp Asn Asp Arg Gly Lys Asn Gln Glu Lys Val Ile Ala Ala
370 375 380

Leu Ile Lys Lys Met Ser Thr Pro Glu Asn Leu Lys Asn Tyr Gln Ala
385 390 395 400

Ile Leu Ser Gly Leu Glu Gly Ser Ile Gln Thr Asp Leu Ser Leu Glu
405 410 415

Thr Ile Met Ser Leu Val Asn Thr Gln Leu Glu Ser Gly Thr Gln Phe
420 425 430

Thr Val Glu Ser Gln Ala Leu Thr Gly Thr Gly Arg Ser Asp Leu Ser
435 440 445

Ser Tyr Ala Met Pro Gly Ser Gln Leu Tyr Met Met Glu Ile Asn Gln
450 455 460

Asp Ser Leu Glu Gln Ser Lys Ala Ala Ile Gln Ser Val Leu Val Glu
465 470 475 480

Lys

<210> 13

<211> 229

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2B

<400> 13

Met Asn Asn Gln Glu Val Asn Ala Ile Glu Ile Asp Val Leu Phe Leu
1 5 10 15

Leu Lys Thr Ile Trp Arg Lys Lys Phe Leu Ile Leu Leu Thr Ala Val
20 25 30

Leu Thr Ala Gly Leu Ala Phe Val Tyr Ser Ser Phe Leu Val Thr Pro
35 40 45

Gln Tyr Asp Ser Thr Thr Arg Ile Tyr Val Val Ser Gln Asn Val Glu
50 55 60

Ala Gly Ala Gly Leu Thr Asn Gln Glu Leu Gln Ala Gly Thr Tyr Leu
65 70 75 80

Ala Lys Asp Tyr Arg Glu Ile Ile Leu Ser Gln Asp Val Leu Thr Gln
85 90 95

Val Ala Thr Glu Leu Asn Leu Lys Glu Ser Leu Lys Glu Lys Ile Ser
100 105 110

Val Ser Ile Pro Val Asp Thr Arg Ile Val Ser Ile Ser Val Arg Asp
115 120 125

Ala Asp Pro Asn Glu Ala Ala Arg Ile Ala Asn Ser Leu Arg Thr Phe
130 135 140

Ala Val Gln Lys Val Val Glu Val Thr Lys Val Ser Asp Val Thr Thr
145 150 155 160

Leu Glu Glu Ala Val Pro Ala Glu Glu Pro Thr Thr Pro Asn Thr Lys
165 170 175

Arg Asn Ile Leu Leu Gly Leu Leu Ala Gly Gly Ile Leu Ala Thr Gly
180 185 190

Leu Val Leu Val Met Glu Val Leu Asp Asp Arg Val Lys Arg Pro Gln
195 200 205

Asp Ile Glu Glu Val Met Gly Leu Thr Leu Leu Gly Ile Val Pro Asp
210 215 220

Ser Lys Lys Leu Lys
225

<210> 14

<211> 225

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2C

<400> 14

Met Ala Met Leu Glu Ile Ala Arg Thr Lys Arg Glu Gly Val Asn Lys
1 5 10 15

Thr Glu Glu Tyr Phe Asn Ala Ile Arg Thr Asn Ile Gln Leu Ser Gly
20 25 30

Ala Asp Ile Lys Val Val Gly Ile Thr Ser Val Lys Ser Asn Glu Gly
35 40 45

Lys Ser Thr Thr Ala Ala Ser Leu Ala Ile Ala Tyr Ala Arg Ser Gly
50 55 60

Tyr Lys Thr Val Leu Val Asp Ala Asp Ile Arg Asn Ser Val Met Pro
65 70 75 80

Gly Phe Phe Lys Pro Ile Thr Lys Ile Thr Gly Leu Thr Asp Tyr Leu
85 90 95

Ala Gly Thr Thr Asp Leu Ser Gln Gly Leu Cys Asp Thr Asp Ile Pro
100 105 110

Asn Leu Thr Val Ile Glu Ser Gly Lys Val Ser Pro Asn Pro Thr Ala
115 120 125

Leu Leu Gln Ser Lys Asn Phe Glu Asn Leu Leu Ala Thr Leu Arg Arg
130 135 140

Tyr Tyr Asp Tyr Val Ile Val Asp Cys Pro Pro Leu Gly Leu Val Ile
145 150 155 160

Asp Ala Ala Ile Ile Ala Gln Lys Cys Asp Ala Met Val Ala Val Val
165 170 175

Glu Ala Gly Asn Val Lys Cys Ser Ser Leu Lys Lys Val Lys Glu Gln
180 185 190

Leu Glu Gln Thr Gly Thr Pro Phe Leu Gly Val Ile Leu Asn Lys Tyr
195 200 205

Asp Ile Ala Thr Glu Lys Tyr Ser Glu Tyr Gly Asn Tyr Gly Lys Lys
210 215 220

Ala
225

<210> 15

<211> 243

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2D

<400> 15

Met Ile Asp Ile His Ser His Ile Ile Phe Gly Val Asp Asp Gly Pro
1 5 10 15

Lys Thr Ile Glu Glu Ser Leu Ser Leu Ile Ser Glu Ala Tyr Arg Gln
20 25 30

Gly Val Arg Tyr Ile Val Ala Thr Ser His Arg Arg Lys Gly Met Phe
35 40 45

Glu Thr Pro Glu Lys Ile Ile Met Ile Asn Phe Leu Gln Leu Lys Glu
50 55 60

Ala Val Ala Glu Val Tyr Pro Glu Ile Arg Leu Cys Tyr Gly Ala Glu
65 70 75 80

Leu Tyr Tyr Ser Lys Asp Ile Leu Ser Lys Leu Glu Lys Lys Lys Val
85 90 95

Pro Thr Leu Asn Gly Ser Cys Tyr Ile Leu Leu Glu Phe Ser Thr Asp
100 105 110

Thr Pro Trp Lys Glu Ile Gln Glu Ala Val Asn Glu Met Thr Leu Leu
115 120 125

Gly Leu Thr Pro Val Leu Ala His Ile Glu Arg Tyr Asp Ala Leu Ala
130 135 140

Phe Gln Ser Glu Arg Val Glu Lys Leu Ile Asp Lys Gly Cys Tyr Thr
145 150 155 160

Gln Val Asn Ser Asn His Val Leu Lys Pro Ala Leu Ile Gly Glu Arg
165 170 175

Ala Lys Glu Phe Lys Lys Arg Thr Arg Tyr Phe Leu Glu Gln Asp Leu
180 185 190

Val His Cys Val Ala Ser Asp Met His Asn Leu Tyr Ser Arg Pro Pro
195 200 205

Phe Met Arg Glu Ala Tyr Gln Leu Val Lys Lys Glu Tyr Gly Glu Asp
210 215 220

Arg Ala Lys Ala Leu Phe Lys Lys Asn Pro Leu Leu Ile Leu Lys Asn
225 230 235 240

Gln Val Gln

<210> 16

<211> 459

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2E

<400> 16

Met Asn Ile Glu Ile Gly Tyr Arg Gln Thr Lys Leu Ala Leu Phe Asp
1 5 10 15

Met Ile Ala Val Thr Ile Ser Ala Ile Leu Thr Ser His Ile Pro Asn
20 25 30

Ala Asp Leu Asn Arg Ser Gly Ile Phe Ile Ile Met Met Val His Tyr
35 40 45

Phe Ala Phe Phe Ile Ser Arg Met Pro Val Glu Phe Glu Tyr Arg Gly
50 55 60

Asn Leu Ile Glu Phe Glu Lys Thr Phe Asn Tyr Ser Ile Ile Phe Val
65 70 75 80

Ile Phe Leu Met Ala Val Ser Phe Met Leu Glu Asn Asn Phe Ala Leu
85 90 95

Ser Arg Arg Gly Ala Val Tyr Phe Thr Leu Ile Asn Phe Val Leu Val
100 105 110

Tyr Leu Phe Asn Val Ile Ile Lys Gln Phe Lys Asp Ser Phe Leu Phe
115 120 125

Ser Thr Thr Tyr Gln Lys Lys Thr Ile Leu Ile Thr Thr Ala Glu Leu
130 135 140

Trp Glu Asn Met Gln Val Leu Phe Glu Ser Asp Ile Leu Phe Gln Lys
145 150 155 160

Asn Leu Val Ala Leu Val Ile Leu Gly Thr Glu Ile Asp Lys Ile Asn
165 170 175

Leu Pro Leu Pro Leu Tyr Tyr Ser Val Glu Glu Ala Ile Gly Phe Ser
180 185 190

Thr Arg Glu Val Val Asp Tyr Val Phe Ile Asn Leu Pro Ser Glu Tyr
195 200 205

Phe Asp Leu Lys Gln Leu Val Ser Asp Phe Glu Leu Leu Gly Ile Asp
210 215 220

Val Gly Val Asp Ile Asn Ser Phe Gly Phe Thr Val Leu Lys Asn Lys
225 230 235 240

Lys Ile Gln Met Leu Gly Asp His Ser Ile Val Thr Phe Ser Thr Asn
245 250 255

Phe Tyr Lys Pro Ser His Ile Trp Met Lys Arg Leu Leu Asp Ile Leu
260 265 270

Gly Ala Val Val Gly Leu Ile Ile Ser Gly Ile Val Ser Ile Leu Leu
275 280 285

Ile Pro Ile Ile Arg Arg Asp Gly Gly Pro Ala Ile Phe Ala Gln Lys
290 295 300

Arg Val Gly Gln Asn Gly Arg Ile Phe Thr Phe Tyr Lys Phe Arg Ser
305 310 315 320

Met Phe Val Asp Ala Glu Val Arg Lys Lys Glu Leu Met Ala Gln Asn
325 330 335

Gln Met Gln Gly Gly Met Phe Lys Met Asp Asn Asp Pro Arg Ile Thr
340 345 350

Pro Ile Gly His Phe Ile Arg Lys Thr Ser Leu Asp Glu Leu Pro Gln
355 360 365

Phe Tyr Asn Val Leu Ile Gly Asp Met Ser Leu Val Gly Thr Arg Pro
370 375 380

Pro Thr Val Asp Glu Phe Glu Lys Tyr Thr Pro Ser Gln Lys Arg Arg
385 390 395 400

Leu Ser Phe Lys Pro Gly Ile Thr Gly Leu Trp Gln Val Ser Gly Arg
405 410 415

Ser Asp Ile Thr Asp Phe Asn Glu Val Val Arg Leu Asp Leu Thr Tyr
420 425 430

Ile Asp Asn Trp Thr Ile Trp Ser Asp Ile Lys Ile Leu Leu Lys Thr
435 440 445

Val Lys Val Val Leu Leu Arg Glu Gly Gly Gln
450 455

<210> 17

<211> 389

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2F

<400> 17

Met Arg Thr Val Tyr Ile Ile Gly Ser Lys Gly Ile Pro Ala Lys Tyr
1 5 10 15

Gly Gly Phe Glu Thr Phe Val Glu Lys Leu Thr Glu Tyr Gln Lys Asp
20 25 30

Lys Ser Ile Asn Tyr Phe Val Ala Cys Thr Arg Glu Asn Ser Ala Lys
35 40 45

Ser Asp Ile Thr Gly Glu Val Phe Glu His Asn Gly Ala Thr Cys Phe
50 55 60

Asn Ile Asp Val Pro Asn Ile Gly Ser Ala Lys Ala Ile Leu Tyr Asp
65 70 75 80

Ile Met Ala Leu Lys Lys Ser Ile Glu Ile Ala Lys Asp Arg Asn Asp
85 90 95

Thr Ser Pro Ile Phe Tyr Ile Leu Ala Cys Arg Ile Gly Pro Phe Ile
100 105 110

Tyr Leu Phe Lys Lys Gln Ile Glu Ser Ile Gly Gly Gln Leu Phe Val
115 120 125

Asn Pro Asp Gly His Glu Trp Leu Arg Glu Lys Trp Ser Tyr Pro Val
130 135 140

Arg Gln Tyr Trp Lys Phe Ser Glu Ser Leu Met Leu Lys Tyr Ala Asp
145 150 155 160

Leu Leu Ile Cys Asp Ser Lys Asn Ile Glu Lys Tyr Ile His Glu Asp
165 170 175

Tyr Arg Lys Tyr Ala Pro Glu Thr Ser Tyr Ile Ala Tyr Gly Thr Asp
180 185 190

Leu Asp Lys Ser Arg Leu Ser Pro Thr Asp Ser Val Val Arg Glu Trp
195 200 205

Tyr Lys Glu Lys Glu Ile Ser Glu Asn Asp Tyr Tyr Leu Val Val Gly
210 215 220

Arg Phe Val Pro Glu Asn Asn Tyr Glu Val Met Ile Arg Glu Phe Met
225 230 235 240

Lys Ser Tyr Ser Arg Lys Asp Phe Val Leu Ile Thr Asn Val Glu His
245 250 255

Asn Ser Phe Tyr Glu Lys Leu Lys Lys Glu Thr Gly Phe Asp Lys Asp
260 265 270

Lys Arg Ile Lys Phe Val Gly Thr Val Tyr Asn Gln Glu Leu Leu Lys
275 280 285

Tyr Ile Arg Glu Asn Ala Phe Ala Tyr Phe His Gly His Glu Val Gly
290 295 300

Gly Thr Asn Pro Ser Leu Leu Glu Ala Leu Ser Ser Thr Lys Leu Asn
305 310 315 320

Leu Leu Leu Asp Val Gly Phe Asn Arg Glu Val Gly Glu Glu Gly Ala
325 330 335

Lys Tyr Trp Asn Lys Asp Asn Leu His Arg Val Ile Asp Ser Cys Glu
340 345 350

Gln Leu Ser Gln Glu Gln Ile Asn Asp Met Asp Ser Leu Ser Thr Lys
355 360 365

Gln Val Lys Glu Arg Phe Ser Trp Asp Phe Ile Val Asp Glu Tyr Glu
370 375 380

Lys Leu Phe Lys Gly
385

<210> 18

<211> 385

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2G

<400> 18

Met Lys Lys Ile Leu Tyr Leu His Ala Gly Ala Glu Leu Tyr Gly Ala
1 5 10 15

Asp Lys Val Leu Leu Glu Leu Ile Lys Gly Leu Asp Lys Asn Glu Phe
20 25 30

Glu Ala His Val Ile Leu Pro Asn Asp Gly Val Leu Val Pro Ala Leu
35 40 45

Arg Glu Val Gly Ala Gln Val Glu Val Ile Asn Tyr Pro Ile Leu Arg
50 55 60

Arg Lys Tyr Phe Asn Pro Lys Gly Ile Phe Asp Tyr Phe Ile Ser Tyr
65 70 75 80

His His Tyr Ser Lys Gln Ile Ala Gln Tyr Ala Ile Glu Asn Lys Val
85 90 95

Asp Ile Ile His Asn Asn Thr Thr Ala Val Leu Glu Gly Ile Tyr Leu
100 105 110

Lys Arg Lys Leu Lys Leu Pro Leu Leu Trp His Val His Glu Ile Ile
115 120 125

Val Lys Pro Lys Phe Ile Ser Asp Ser Ile Asn Phe Leu Met Gly Arg
130 135 140

Phe Ala Asp Lys Ile Val Thr Val Ser Gln Ala Val Ala Asn His Ile
145 150 155 160

Lys Gln Ser Pro His Ile Lys Asp Asp Gln Ile Ser Val Ile Tyr Asn
165 170 175

Gly Val Asp Asn Lys Val Phe Tyr Gln Ser Asp Ala Arg Ser Val Arg
180 185 190

Glu Arg Phe Asp Ile Asp Glu Glu Ala Leu Val Ile Gly Met Val Gly
195 200 205

Arg Val Asn Ala Trp Lys Gly Gln Gly Asp Phe Leu Glu Ala Val Ala
210 215 220

Pro Ile Leu Glu Gln Asn Pro Lys Ala Ile Ala Phe Ile Ala Gly Ser
225 230 235 240

Ala Phe Glu Gly Glu Glu Trp Arg Val Val Glu Leu Glu Lys Lys Ile
245 250 255

Ser Gln Leu Lys Val Ser Ser Gln Val Arg Arg Met Asp Tyr Tyr Ala
260 265 270

Asn Thr Thr Glu Leu Tyr Asn Met Phe Asp Ile Phe Val Leu Pro Ser
275 280 285

Thr Asn Pro Asp Pro Leu Pro Thr Val Val Leu Lys Ala Met Ala Cys
290 295 300

Gly Lys Pro Val Val Gly Tyr Arg His Gly Gly Val Cys Glu Met Val
305 310 315 320

Lys Glu Gly Val Asn Gly Phe Leu Val Thr Pro Asn Ser Pro Leu Asn
325 330 335

Leu Ser Lys Val Ile Leu Gln Leu Ser Glu Asn Ile Asn Leu Arg Lys
340 345 350

Lys Ile Gly Asn Asn Ser Ile Glu Arg Gln Lys Glu His Phe Ser Leu
355 360 365

Lys Ser Tyr Val Lys Asn Phe Ser Lys Val Tyr Thr Ser Leu Lys Val
370 375 380

Tyr
385

<210> 19

<211> 456

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> cps2h

<400> 19

Met Lys Ile Ile Ser Phe Thr Met Val Asn Asn Glu Ser Glu Ile Ile
1 5 10 15

Glu Ser Phe Ile Arg Tyr Asn Tyr Asn Phe Ile Asp Glu Met Val Ile
20 25 30

Ile Asp Asn Gly Cys Thr Asp Asn Thr Met Gln Ile Ile Phe Asn Leu
35 40 45

Ile Lys Glu Gly Tyr Lys Ile Ser Val Tyr Asp Glu Ser Leu Glu Ala
50 55 60

Tyr Asn Gln Tyr Arg Leu Asp Asn Lys Tyr Leu Thr Lys Ile Ile Ala
65 70 75 80

Glu Lys Asn Pro Asp Leu Ile Ile Pro Leu Asp Ala Asp Glu Phe Leu
85 90 95

Thr Ala Asp Ser Asn Pro Arg Lys Leu Leu Glu Gln Leu Asp Leu Glu
100 105 110

Lys Ile His Tyr Val Asn Trp Gln Trp Phe Val Met Thr Lys Lys Asp
115 120 125

Asp Ile Asn Asp Ser Phe Ile Pro Arg Arg Met Gln Tyr Cys Phe Glu
130 135 140

Lys Pro Val Trp His His Ser Asp Gly Lys Pro Val Thr Lys Cys Ile
145 150 155 160

Ile Ser Ala Lys Tyr Tyr Lys Lys Met Asn Leu Lys Leu Ser Met Gly
165 170 175

His His Thr Val Phe Gly Asn Pro Asn Val Arg Ile Glu His His Asn
180 185 190

Asp Leu Lys Phe Ala His Tyr Arg Ala Ile Ser Gln Glu Gln Leu Ile
195 200 205

Tyr Lys Thr Ile Cys Tyr Thr Ile Arg Asp Ile Ala Thr Met Glu Asn
210 215 220

Asn Ile Glu Thr Ala Gln Arg Thr Asn Gln Met Ala Leu Ile Glu Ser
225 230 235 240

Gly Val Asp Met Trp Glu Thr Ala Arg Glu Ala Ser Tyr Ser Gly Tyr
245 250 255

Asp Cys Asn Val Ile His Ala Pro Ile Asp Leu Ser Phe Cys Lys Glu
260 265 270

Asn Ile Val Ile Lys Tyr Asn Glu Leu Ser Arg Glu Thr Val Ala Glu
275 280 285

Arg Val Met Lys Thr Gly Arg Glu Met Ala Val Arg Ala Tyr Asn Val
290 295 300

Glu Arg Lys Gln Lys Glu Lys Lys Phe Leu Lys Pro Ile Ile Phe Val
305 310 315 320

Leu Asp Gly Leu Lys Gly Asp Glu Tyr Ile His Pro Asn Pro Ser Asn
325 330 335

His Leu Thr Ile Leu Thr Glu Met Tyr Asn Val Arg Gly Leu Leu Thr
340 345 350

Asp Asn His Gln Ile Lys Phe Leu Lys Val Asn Tyr Arg Leu Ile Ile
355 360 365

Thr Pro Asp Phe Ala Lys Phe Leu Pro His Glu Phe Ile Val Val Pro
370 375 380

Asp Thr Leu Asp Ile Glu Gln Val Lys Ser Gln Tyr Val Gly Thr Gly
385 390 395 400

Val Asp Leu Ser Lys Ile Ile Ser Leu Lys Glu Tyr Arg Lys Glu Ile
405 410 415

Gly Phe Ile Gly Asn Leu Tyr Ala Leu Leu Gly Phe Val Pro Asn Met
420 425 430

Leu Asn Arg Ile Tyr Leu Tyr Ile Gln Arg Asn Gly Ile Ala Asn Thr
435 440 445

Ile Ile Lys Ile Lys Ser Arg Leu
450 455

<210> 20

<211> 410

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2I

<400> 20

Met Gln Ala Asp Arg Arg Lys Thr Phe Gly Lys Met Arg Ile Arg Ile
1 5 10 15

Asn Asn Leu Phe Phe Val Ala Ile Ala Phe Met Gly Ile Ile Ile Ser
20 25 30

Asn Ser Gln Val Val Leu Ala Ile Gly Lys Ala Ser Val Ile Gln Tyr
35 40 45

Leu Ser Tyr Leu Val Leu Ile Leu Cys Ile Val Asn Asp Leu Leu Lys
50 55 60

Asn Asn Lys His Ile Val Val Tyr Lys Leu Gly Tyr Leu Phe Leu Ile
65 70 75 80

Ile Phe Leu Phe Thr Ile Gly Ile Cys Gln Gln Ile Leu Pro Ile Thr
85 90 95

Thr Lys Ile Tyr Leu Ser Ile Ser Met Met Ile Ile Ser Val Leu Ala
100 105 110

Thr Leu Pro Ile Ser Leu Ile Lys Asp Ile Asp Asp Phe Arg Arg Ile
115 120 125

Ser Asn His Leu Leu Phe Ala Leu Phe Ile Thr Ser Ile Leu Gly Ile
130 135 140

Lys Met Gly Ala Thr Met Phe Thr Gly Ala Val Glu Gly Ile Gly Phe
145 150 155 160

Ser Gln Gly Phe Asn Gly Gly Leu Thr His Lys Asn Phe Phe Gly Ile
165 170 175

Thr Ile Leu Met Gly Phe Val Leu Thr Tyr Leu Ala Tyr Lys Tyr Gly
180 185 190

Ser Tyr Lys Arg Thr Asp Arg Phe Ile Leu Gly Leu Glu Leu Phe Leu
195 200 205

Ile Leu Ile Ser Asn Thr Arg Ser Val Tyr Leu Ile Leu Leu Leu Phe
210 215 220

Leu Phe Leu Val Asn Leu Asp Lys Ile Lys Ile Glu Gln Arg Gln Trp
225 230 235 240

Ser Thr Leu Lys Tyr Ile Ser Met Leu Phe Cys Ala Ile Phe Leu Tyr
245 250 255

Tyr Phe Phe Gly Phe Leu Ile Thr His Ser Asp Ser Tyr Ala His Arg
260 265 270

Val Asn Gly Leu Ile Asn Phe Phe Glu Tyr Tyr Arg Asn Asp Trp Phe
275 280 285

His Leu Met Phe Gly Ala Ala Asp Leu Ala Tyr Gly Asp Leu Thr Leu
290 295 300

Asp Tyr Ala Ile Arg Val Arg Arg Val Leu Gly Trp Asn Gly Thr Leu
305 310 315 320

Glu Met Pro Leu Leu Ser Ile Met Leu Lys Asn Gly Phe Ile Gly Leu
325 330 335

Val Gly Tyr Gly Ile Val Leu Tyr Lys Leu Tyr Arg Asn Val Arg Ile
340 345 350

Leu Lys Thr Asp Asn Ile Lys Thr Ile Gly Lys Ser Val Phe Ile Ile
355 360 365

Val Val Leu Ser Ala Thr Val Glu Asn Tyr Ile Val Asn Leu Ser Phe
370 375 380

Val Phe Met Pro Ile Cys Phe Cys Leu Leu Asn Ser Ile Ser Thr Met
385 390 395 400

Glu Ser Thr Ile Asn Lys Gln Leu Gln Thr
405 410

<210> 21

<211> 332

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2J

<400> 21

Met Glu Lys Val Ser Ile Ile Val Pro Ile Phe Asn Thr Glu Lys Tyr
1 5 10 15

Leu Arg Glu Cys Leu Asp Ser Ile Ile Ser Gln Ser Tyr Thr Asn Leu
20 25 30

Glu Ile Leu Leu Ile Asp Asp Gly Ser Ser Asp Ser Ser Thr Asp Ile
35 40 45

Cys Leu Glu Tyr Ala Glu Gln Asp Gly Arg Ile Lys Leu Phe Arg Leu
50 55 60

Pro Asn Gly Gly Val Ser Asn Ala Arg Asn Tyr Gly Ile Lys Asn Ser
65 70 75 80

Thr Ala Asn Tyr Ile Met Phe Val Asp Ser Asp Asp Ile Val Asp Gly
85 90 95

Asn Ile Val Glu Ser Leu Tyr Thr Cys Leu Lys Glu Asn Asp Ser Asp
100 105 110

Leu Ser Gly Gly Leu Leu Ala Thr Phe Asp Gly Asn Tyr Gln Glu Ser
115 120 125

Glu Leu Gln Lys Cys Gln Ile Asp Leu Glu Glu Ile Lys Glu Val Arg
130 135 140

Asp Leu Gly Asn Glu Asn Phe Pro Asn His Tyr Met Ser Gly Ile Phe
145 150 155 160

Asn Ser Pro Cys Cys Lys Leu Tyr Lys Asn Ile Tyr Ile Asn Gln Gly
165 170 175

Phe Asp Thr Glu Gln Trp Leu Gly Glu Asp Leu Leu Phe Asn Leu Asn
180 185 190

Tyr Leu Lys Asn Ile Lys Lys Val Arg Tyr Val Asn Arg Asn Leu Tyr
195 200 205

Phe Ala Arg Arg Ser Leu Gln Ser Thr Thr Asn Thr Phe Lys Tyr Asp
210 215 220

Val Phe Ile Gln Leu Glu Asn Leu Glu Glu Lys Thr Phe Asp Leu Phe
225 230 235 240

Val Lys Ile Phe Gly Gly Gln Tyr Glu Phe Ser Val Phe Lys Glu Thr
245 250 255

Leu Gln Trp His Ile Ile Tyr Tyr Ser Leu Leu Met Phe Lys Asn Gly
260 265 270

Asp Glu Ser Leu Pro Lys Lys Leu His Ile Phe Lys Tyr Leu Tyr Asn
275 280 285

Arg His Ser Leu Asp Thr Leu Ser Ile Lys Arg Thr Ser Ser Val Phe
290 295 300

Lys Arg Ile Cys Lys Leu Ile Val Ala Asn Asn Leu Phe Lys Ile Phe
305 310 315 320

Leu Asn Thr Leu Ile Arg Glu Glu Lys Asn Asn Asp
325 330

<210> 22

<211> 332

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2K

<400> 22

Met Ile Asn Ile Ser Ile Ile Val Pro Ile Tyr Asn Val Glu Gln Tyr
1 5 10 15

Leu Ser Lys Cys Ile Asn Ser Ile Val Asn Gln Thr Tyr Lys His Ile
20 25 30

Glu Ile Leu Leu Val Asn Asp Gly Ser Thr Asp Asn Ser Glu Glu Ile
35 40 45

Cys Leu Ala Tyr Ala Lys Lys Asp Ser Arg Ile Arg Tyr Phe Lys Lys
50 55 60

Glu Asn Gly Gly Leu Ser Asp Ala Arg Asn Tyr Gly Ile Ser Arg Ala
65 70 75 80

Lys Gly Asp Tyr Leu Ala Phe Ile Asp Ser Asp Asp Phe Ile His Ser
85 90 95

Glu Phe Ile Gln Arg Leu His Glu Ala Ile Glu Arg Glu Asn Ala Leu
100 105 110

Val Ala Val Ala Gly Tyr Asp Arg Val Asp Ala Ser Gly His Phe Leu
115 120 125

Thr Ala Glu Pro Leu Pro Thr Asn Gln Ala Val Leu Ser Gly Arg Asn
130 135 140

Val Cys Lys Lys Leu Leu Glu Ala Asp Gly His Arg Phe Val Val Ala
145 150 155 160

Trp Asn Lys Leu Tyr Lys Lys Glu Leu Phe Asp Phe Arg Phe Glu Lys
165 170 175

Gly Lys Ile His Glu Asp Glu Tyr Phe Thr Tyr Arg Leu Leu Tyr Glu
180 185 190

Leu Glu Lys Val Ala Ile Val Lys Glu Cys Leu Tyr Tyr Tyr Val Asp
195 200 205

Arg Glu Asn Ser Ile Ile Thr Ser Ser Met Thr Asp His Arg Phe His
210 215 220

Cys Leu Leu Glu Phe Gln Asn Glu Arg Met Asp Phe Tyr Glu Ser Arg
225 230 235 240

Gly Asp Lys Glu Leu Leu Leu Glu Cys Tyr Arg Ser Phe Leu Ala Phe
245 250 255

Ala Val Leu Phe Leu Gly Lys Tyr Asn His Trp Leu Ser Lys Gln Gln
260 265 270

Lys Lys Leu Gln Thr Leu Phe Arg Ile Val Tyr Lys Gln Leu Lys Gln
275 280 285

Asn Lys Arg Leu Ala Leu Leu Met Asn Ala Tyr Tyr Leu Val Gly Cys
290 295 300

Leu His Leu Asn Phe Ser Val Phe Leu Lys Thr Gly Lys Asp Lys Ile
305 310 315 320

Gln Glu Arg Leu Arg Arg Ser Glu Ser Ser Thr Arg
325 330

<210> 23

<211> 467

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2O

<220>

<221> misc_feature

<222> (1)..(467)

<223> Xaa may be any amino acid

<400> 23

Met Ser Lys Lys Ser Ile Val Val Ser Gly Leu Val Tyr Thr Ile Gly
1 5 10 15

Thr Ile Leu Val Gln Gly Leu Ala Phe Ile Thr Leu Pro Ile Tyr Thr
20 25 30

Arg Val Ile Ser Gln Glu Val Tyr Gly Gln Phe Ser Leu Tyr Asn Ser
35 40 45

Trp Val Gly Leu Val Gly Leu Phe Ile Gly Leu Gln Leu Gly Gly Ala
50 55 60

Phe Gly Pro Gly Trp Val His Phe Arg Glu Lys Phe Asp Asp Phe Val
65 70 75 80

Ser Thr Leu Met Val Ser Ser Ile Ala Phe Phe Leu Pro Ile Phe Gly
85 90 95

Leu Ser Phe Leu Leu Ser Gln Pro Leu Ser Leu Leu Phe Gly Leu Pro
100 105 110

Asp Trp Val Val Pro Leu Ile Phe Leu Gln Ser Leu Met Ile Val Val
115 120 125

Gln Gly Phe Phe Thr Thr Tyr Leu Val Gln Arg Gln Gln Ser Met Trp
130 135 140

Thr Leu Pro Leu Ser Val Leu Ser Ala Val Ile Asn Thr Ala Leu Ser
145 150 155 160

Leu Phe Leu Thr Phe Pro Met Glu Asn Asp Phe Ile Ala Arg Val Met
165 170 175

Ala Asn Pro Ala Thr Thr Gly Val Leu Ala Cys Val Ser Xaa Trp Phe
180 185 190

Ser Gln Lys Lys Asn Gly Leu His Phe Arg Lys Asp Tyr Leu Arg Tyr
195 200 205

Gly Leu Ser Ile Ser Ile Pro Leu Ile Phe His Gly Leu Gly His Asn
210 215 220

Val Leu Asn Gln Phe Asp Arg Ile Met Leu Gly Lys Met Leu Thr Leu
225 230 235 240

Ser Asp Val Ala Leu Tyr Ser Phe Gly Tyr Thr Leu Ala Ser Ile Leu
245 250 255

Gln Ile Val Phe Ser Ser Leu Asn Thr Val Trp Cys Pro Trp Tyr Phe
260 265 270

Glu Lys Lys Arg Gly Ala Asp Lys Asp Leu Leu Ser Tyr Val Arg Tyr
275 280 285

Tyr Leu Ala Ile Gly Leu Phe Val Thr Phe Gly Phe Leu Thr Ile Tyr
290 295 300

Pro Arg Leu Ala Met Leu Leu Gly Gly Ser Glu Tyr Arg Phe Ser Met
305 310 315 320

Gly Phe Ile Pro Met Ile Ile Val Gly Val Phe Phe Val Phe Leu Tyr
325 330 335

Ser Phe Pro Ala Asn Ile Gln Phe Tyr Ser Gly Asn Thr Lys Phe Leu
340 345 350

Pro Ile Gly Thr Phe Ile Ala Gly Val Leu Asn Ile Ser Val His Phe
355 360 365

Val Leu Ile Pro Thr Lys Asn Leu Trp Cys Cys Phe Ala Thr Thr Ala
370 375 380

Ser Tyr Leu Leu Leu Leu Val Leu His Tyr Phe Val Ala Lys Lys Lys
385 390 395 400

Tyr Ala Tyr Asp Glu Val Ala Ile Ser Thr Phe Val Lys Val Ile Ala
405 410 415

Leu Val Val Val Tyr Thr Gly Leu Met Thr Val Phe Val Gly Ser Ile
420 425 430

Trp Ile Arg Trp Ser Leu Gly Ile Ala Val Leu Val Val Tyr Ala Ile
435 440 445

Tyr Phe Arg Lys Glu Leu Thr Val Ala Leu Asn Thr Phe Arg Glu Lys
450 455 460

Arg Ser Lys
465

<210> 24

<211> 338

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2P

<400> 24

Met Val Tyr Ile Ile Ala Glu Ile Gly Cys Asn His Asn Gly Asp Val
1 5 10 15

His Leu Ala Arg Lys Met Val Glu Val Ala Val Asp Cys Gly Val Asp
20 25 30

Ala Val Lys Phe Gln Thr Glu Lys Ala Asp Leu Leu Ile Ser Lys Tyr
35 40 45

Ala Pro Lys Ala Glu Tyr Gln Lys Ile Thr Thr Gly Glu Ser Asp Ser
50 55 60

Gln Leu Glu Met Thr Arg Arg Leu Glu Leu Ser Phe Glu Glu Tyr Leu
65 70 75 80

Asp Leu Arg Asp Tyr Cys Leu Glu Lys Gly Val Asp Val Phe Ser Thr
85 90 95

Pro Glu Asp Glu Glu Ser Leu Asp Phe Leu Ile Ser Thr Asp Met Pro
100 105 110

Val Tyr Lys Ile Pro Ser Gly Glu Ile Thr Asn Leu Pro Tyr Leu Glu
115 120 125

Lys Ile Gly Arg Gln Ala Lys Lys Val Ile Leu Ser Thr Gly Met Ala
130 135 140

Val Met Asp Glu Ile His Gln Ala Val Lys Ile Leu Gln Glu Asn Gly
145 150 155 160

Thr Thr Asp Ile Ser Ile Leu His Cys Thr Thr Glu Tyr Pro Thr Pro
165 170 175

Tyr Pro Ala Leu Asn Leu Asn Val Leu His Thr Leu Lys Lys Glu Phe
180 185 190

Pro Asn Leu Thr Ile Gly Tyr Ser Asp His Ser Val Gly Ser Glu Val
195 200 205

Pro Ile Ala Ala Ala Ala Met Gly Ala Glu Leu Ile Glu Lys His Phe
210 215 220

Thr Leu Asp Asn Glu Met Glu Gly Pro Asp His Lys Ala Ser Ala Thr
225 230 235 240

Pro Asp Ile Leu Ala Ala Leu Val Lys Gly Val Arg Ile Val Glu Gln
245 250 255

Ser Leu Gly Lys Phe Glu Lys Glu Pro Glu Glu Val Glu Val Arg Asn
260 265 270

Lys Ile Val Ala Glu Lys Ser Ile Val Ala Lys Lys Ala Ile Ala Lys
275 280 285

Gly Glu Val Phe Thr Glu Glu Asn Ile Thr Val Lys Arg Pro Gly Asn
290 295 300

Gly Ile Ser Pro Met Glu Trp Tyr Lys Val Leu Gly Gln Val Ser Glu
305 310 315 320

Gln Asp Phe Glu Glu Asp Gln Asn Ile Cys His Ser Ala Phe Glu Asn
325 330 335

Gln Met

<210> 25

<211> 170

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2Q

<400> 25

Met Lys Lys Ile Cys Phe Val Thr Gly Ser Arg Ala Glu Tyr Gly Ile
1 5 10 15

Met Arg Arg Leu Leu Ser Tyr Leu Gln Asp Asp Pro Glu Met Glu Leu
20 25 30

Asp Leu Val Val Ala Thr Met His Leu Glu Glu Lys Tyr Gly Met Thr
35 40 45

Val Lys Asp Ile Glu Ala Asp Lys Arg Arg Ile Val Lys Arg Ile Pro
50 55 60

Leu His Leu Thr Asp Thr Ser Lys Gln Thr Ile Val Lys Ser Leu Ala
65 70 75 80

Thr Leu Thr Glu Gln Leu Thr Val Leu Phe Glu Glu Val Gln Tyr Asp
85 90 95

Leu Val Leu Ile Leu Gly Asp Arg Tyr Glu Met Leu Pro Val Ala Asn
100 105 110

Ala Ala Leu Leu Tyr Asn Ile Pro Ile Cys His Ile His Gly Gly Glu
115 120 125

Lys Thr Met Gly Asn Phe Asp Glu Ser Ile Arg His Ala Ile Thr Lys
130 135 140

Met Ser His Leu His Leu Thr Ser Thr Asp Glu Phe Arg Asn Arg Val
145 150 155 160

Ile Gln Leu Gly Glu Asn Pro Thr Met Tyr
165 170

<210> 26

<211> 184

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2R

<400> 26

Met Glu Leu Gly Ile Asp Phe Ala Glu Asp Tyr Tyr Val Val Leu Phe
1 5 10 15

His Pro Val Thr Leu Glu Asp Asn Thr Ala Glu Glu Gln Thr Gln Ala
20 25 30

Leu Leu Asp Ala Leu Lys Glu Asp Gly Ser Gln Cys Leu Ile Ile Gly
35 40 45

Ser Asn Ser Asp Thr His Ala Asp Lys Ile Met Glu Leu Met His Glu
50 55 60

Phe Val Lys Gln Asp Ser Asp Ser Tyr Ile Phe Thr Ser Leu Pro Thr
65 70 75 80

Arg Tyr Tyr His Ser Leu Val Lys His Ser Gln Gly Leu Ile Gly Asn
85 90 95

Ser Ser Ser Gly Leu Ile Glu Val Pro Ser Leu Gln Val Pro Thr Leu
100 105 110

Asn Ile Gly Asn Arg Gln Phe Gly Arg Leu Ser Gly Pro Ser Val Val
115 120 125

His Val Gly Thr Ser Lys Glu Ala Ile Val Gly Gly Leu Gly Gln Leu
130 135 140

Arg Asp Val Ile Asp Phe Thr Asn Pro Phe Glu Gln Pro Asp Ser Ala
145 150 155 160

Leu Gln Gly Tyr Arg Ala Ile Lys Glu Phe Leu Ser Val Gln Ala Ser
165 170 175

Thr Met Lys Glu Phe Tyr Asp Arg
180

<210> 27

<211> 208

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2S

<400> 27

Met Lys Lys Val Ala Phe Leu Gly Ala Gly Thr Phe Ser Asp Gly Val
1 5 10 15

Leu Pro Trp Leu Asp Arg Thr Arg Tyr Glu Leu Ile Gly Tyr Phe Glu
20 25 30

Asp Lys Pro Ile Ser Asp Tyr Arg Gly Tyr Pro Val Phe Gly Pro Leu
35 40 45

Gln Asp Val Leu Thr Tyr Leu Asp Asp Gly Lys Val Asp Ala Val Phe
50 55 60

Val Thr Ile Gly Asp Asn Val Lys Arg Lys Glu Ile Phe Asp Leu Leu
65 70 75 80

Ala Lys Asp His Tyr Asp Ala Leu Phe Asn Ile Ile Ser Glu Gln Ala
85 90 95

Asn Ile Phe Ser Pro Asp Ser Ile Lys Gly Arg Gly Val Phe Ile Gly
100 105 110

Phe Ser Ser Phe Val Gly Ala Asp Ser Tyr Val Tyr Asp Asn Cys Ile
115 120 125

Ile Asn Thr Gly Ala Ile Val Glu His His Thr Thr Val Glu Ala His
130 135 140

Cys Asn Ile Thr Pro Gly Val Thr Ile Asn Gly Leu Cys Arg Ile Gly
145 150 155 160

Glu Ser Thr Tyr Ile Gly Ser Gly Ser Thr Val Ile Gln Cys Ile Glu
165 170 175

Ile Ala Pro Tyr Thr Thr Leu Gly Ala Gly Thr Val Val Leu Lys Ser
180 185 190

Leu Thr Glu Ser Gly Thr Tyr Val Gly Val Pro Ala Arg Lys Ile Lys
195 200 205

<210> 28

<211> 410

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2T

<400> 28

Met Glu Pro Ile Cys Leu Ile Pro Ala Arg Ser Gly Ser Lys Gly Leu
1 5 10 15

Pro Asn Lys Asn Met Leu Phe Leu Asp Gly Val Pro Met Ile Phe His
20 25 30

Thr Ile Arg Ala Ala Ile Glu Ser Gly Cys Phe Lys Lys Glu Asn Ile
35 40 45

Tyr Val Ser Thr Asp Ser Glu Val Tyr Lys Glu Ile Cys Glu Thr Thr
50 55 60

Gly Val Gln Val Leu Met Arg Pro Ala Asp Leu Ala Thr Asp Phe Thr
65 70 75 80

Thr Ser Phe Gln Leu Asn Glu His Phe Leu Gln Asp Phe Ser Asp Asp
85 90 95

Gln Val Phe Val Leu Leu Gln Val Thr Ser Pro Leu Arg Ser Gly Lys
100 105 110

His Val Lys Glu Ala Met Glu Leu Tyr Gly Lys Gly Gln Ala Asp His
115 120 125

Val Val Ser Phe Thr Lys Val Asp Lys Ser Pro Thr Leu Phe Ser Thr
130 135 140

Leu Asp Glu Asn Gly Phe Ala Lys Asp Ile Ala Gly Leu Gly Gly Ser
145 150 155 160

Tyr Arg Arg Gln Asp Glu Lys Thr Leu Tyr Tyr Pro Asn Gly Ala Ile
165 170 175

Tyr Ile Ser Ser Lys Gln Ala Tyr Leu Ala Asp Lys Thr Tyr Phe Ser
180 185 190

Glu Lys Thr Ala Ala Tyr Val Met Thr Lys Glu Asp Ser Ile Asp Val
195 200 205

Asp Asp His Phe Asp Phe Thr Gly Val Ile Gly Arg Ile Tyr Phe Asp
210 215 220

Tyr Gln Arg Arg Glu Gln Gln Asn Lys Pro Phe Tyr Lys Arg Glu Leu
225 230 235 240

Lys Arg Leu Cys Glu Gln Arg Val His Asp Ser Leu Val Ile Gly Asp
245 250 255

Ser Arg Leu Leu Ala Leu Leu Leu Asp Gly Phe Asp Asn Ile Ser Ile
260 265 270

Gly Gly Met Thr Ala Ser Thr Ser Leu Glu Asn Gln Gly Leu Phe Leu
275 280 285

Ala Thr Pro Ile Lys Lys Val Leu Leu Ser Leu Gly Val Asn Asp Leu
290 295 300

Ile Thr Asp Tyr Pro Leu His Met Ile Glu Asp Thr Ile Arg Gln Leu
305 310 315 320

Met Glu Ser Leu Val Ser Lys Ala Glu Gln Val Glu Val Thr Thr Ile
325 330 335

Ala Tyr Thr Leu Phe Arg Asp Ser Val Ser Asn Glu Glu Thr Val Gln
340 345 350

Leu Asn Asp Val Ile Val Gln Ser Ala Ser Glu Leu Gly Ile Ser Val
355 360 365

Ile Asp Leu Asn Glu Val Val Glu Lys Glu Ala Met Leu Asp Tyr Gln
370 375 380

Tyr Thr Asn Asp Gly Leu His Phe Asn Gln Ile Gly Gln Glu Arg Val
385 390 395 400

Asn Gln Leu Ile Leu Thr Ser Leu Thr Arg
405 410

<210> 29

<211> 6992

<212> DNA

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS1

<400> 29

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attattttgc atttttttata tctcgtatgc cagttgaatt tgagtataga ggtaatctga 180

tagagtttga aaaaacattt aactatagta taatatttgc aatttttctt acggcagtat 240

cattttgtt ggagaataat ttcgcacttt caagacgtgg tgccgtgtat ttcacattaa 300

taaacttcgt tttggtatac ctatttaacg taattattaa gcagtttaag gatagctttc 360

tattttcgac aatctatcaa aaaaagacga ttctaattac aacggctgaa cgatgggaaa 420

atatgcaagt tttatttgaa tcacataaac aaattcaaaa aaatcttgtt gcattggtag 480

ttttaggtac agaaatagat aaaattaatt tatcattacc gctctattat tctgtggaag 540

aagctataga gttttcaaca agggaagtgg tcgaccacgt ctttataaat ctaccaagtg 600

agtttttaga cgtaaagcaa ttcgtttcag attttgagtt gttaggtatt gatgtaagcg 660

ttgatattaa ttcattcggt tttactgcgt tgaaaaacaa aaaaatccaa ctgctaggtg 720

accatagcat tgtaactttt tccacaaatt tttataagcc tagtcatatc atgatgaaac 780

gacttttgga tatactcgga gcggtagtcg ggttaattat ttgtggtata gtttctattt 840

tgttagttcc aattattcgt agagatggtg gaccggctat ttttgctcag aaacgagttg 900

gacagaatgg acgcatattt acattctaca agtttcgatc gatgtatgtt gatgctgagg 960

agcgcaaaaa agacttgctc agccaaaacc agatgcaagg gtgggtatgt tttaaaatgg 1020

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agttaccaca gttttataat gttttaattg gcgatatgag tctagttggt acacgtccac 1140

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cagggattac aggtctctgg caggttagtg gtcgtagtaa tatcacagac ttcgacgacg 1260

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tattaaagac agtgaaagtt gtattgttga gagagggaag taagtaaaag tatatgaaag 1380

tttgtttggt cggttcttca gggggacatt tgactcactt gtatttgtta aaaccgtttt 1440

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agaatgaaaa aatgtatcca tgttactttc caacaaatcg caatctcatt aatttagtga 1560

aaaatacttt cttagctttc aaaattttac gtgatgagaa accagatgtt attatttcat 1620

ctggtgcggc cgttgctgtc cccttctttt acatcggaaa actatttgga gcaaagacga 1680

tttatattga agtatttgat cgagttaata aatctacatt aactggaaaa ctagtttatc 1740

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ttaacttggg gagtattttt taatgatttt tgtaacagta ggaactcatg aacaacagtt 1860

taatcgattg ataaaagaga ttgatttatt gaaaaaaaat ggaagtataa ccgacgaaat 1920

atttattcaa acaggatatt ctgactatat tccagaatat tgcaagtata aaaaatttct 1980

cagttacaaa gaaatggaac aatatattaa caaatcagaa gtagttattt gccacggagg 2040

ccccgctact tttatgaatt cattatccaa aggaaaaaaa caattattgt ttcctagaca 2100

aaaaaagtat ggtgaacatg taaatgatca tcaagtagag tttgtaagaa gaatttttaca 2160

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actgtttaga attttattaa gaatgtatcg agcttttgaa tactatttac aaagattgtt 2640

gtttattgat agaataaaaa acatggtcta agaataagat ttggttctaa ttgggtttcg 2700

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aaaaaataaa atagttgatt ttgtgagagt aatgtatgtt taaattattt aaatatgacc 3060

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aattgcttta ccatgaaatt ttggctgttt ataattctag agaatcaagt aacgaagcta 3840

gatttattat ttatcaagga agtattgata aagtattaga aaacaatatt ttatttggat 3900

atggaatatc cgaatattca gttacgggaa cttggctcgg aagtcattca ggctatatat 3960

catttttta taaatcagga atagttgggt tgattttact gatgttttct ttttttatg 4020

ttataaaaaa aagttatgga gttaatgggg aaacagcact attttatttt acatcattag 4080

ccatattttt catatatgaa acaatagatc cgattattat tatattagta ctattctttt 4140

cttcaatagg tatttggaat aatataaatt ttaaaaagga tatggagaca aaaaatgaat 4200

gatttaattt cagttattgt accaatttat aatgtccaag attatcttga taaatgtatt 4260

aacagtatta ttaaccaaac atatactaat ttagaggtta ttctcgtaaa tgatggaagt 4320

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<211> 454

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS1E

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Ala Ile Leu Thr Ser His Ile Pro Asn Ala Asp Leu Asn Arg Ser Gly
20 25 30

Ile Phe Ile Ile Met Met Val His Tyr Phe Ala Phe Phe Ile Ser Arg
35 40 45

Met Pro Val Glu Phe Glu Tyr Arg Gly Asn Leu Ile Glu Phe Glu Lys
50 55 60

Thr Phe Asn Tyr Ser Ile Ile Phe Ala Ile Phe Leu Thr Ala Val Ser
65 70 75 80

Phe Leu Leu Glu Asn Asn Phe Ala Leu Ser Arg Arg Gly Ala Val Tyr
85 90 95

Phe Thr Leu Ile Asn Phe Val Leu Val Tyr Leu Phe Asn Val Ile Ile
100 105 110

Lys Gln Phe Lys Asp Ser Phe Leu Phe Ser Thr Ile Tyr Gln Lys Lys
115 120 125

Thr Ile Leu Ile Thr Thr Ala Glu Arg Trp Glu Asn Met Gln Val Leu
130 135 140

Phe Glu Ser His Lys Gln Ile Gln Lys Asn Leu Val Ala Leu Val Val
145 150 155 160

Leu Gly Thr Glu Ile Asp Lys Ile Asn Leu Ser Leu Pro Leu Tyr Tyr
165 170 175

Ser Val Glu Glu Ala Ile Glu Phe Ser Thr Arg Glu Val Val Asp His
180 185 190

Val Phe Ile Asn Leu Pro Ser Glu Phe Leu Asp Val Lys Gln Phe Val
195 200 205

Ser Asp Phe Glu Leu Leu Gly Ile Asp Val Ser Val Asp Ile Asn Ser
210 215 220

Phe Gly Phe Thr Ala Leu Lys Asn Lys Lys Ile Gln Leu Leu Gly Asp
225 230 235 240

His Ser Ile Val Thr Phe Ser Thr Asn Phe Tyr Lys Pro Ser His Ile
245 250 255

Met Met Lys Arg Leu Leu Asp Ile Leu Gly Ala Val Val Gly Leu Ile
260 265 270

Ile Cys Gly Ile Val Ser Ile Leu Leu Val Pro Ile Ile Arg Arg Asp
275 280 285

Gly Gly Pro Ala Ile Phe Ala Gln Lys Arg Val Gly Gln Asn Gly Arg
290 295 300

Ile Phe Thr Phe Tyr Lys Phe Arg Ser Met Tyr Val Asp Ala Glu Glu
305 310 315 320

Arg Lys Lys Asp Leu Leu Ser Gln Asn Gln Met Gln Gly Trp Val Cys
325 330 335

Phe Lys Met Gly Lys Thr Ile Leu Glu Leu Leu Gln Leu Asp Ile Ser
340 345 350

Tyr Ala Lys Thr Ser Leu Asp Glu Leu Pro Gln Phe Tyr Asn Val Leu
355 360 365

Ile Gly Asp Met Ser Leu Val Gly Thr Arg Pro Pro Thr Val Asp Glu
370 375 380

Phe Glu Lys Tyr Thr Pro Gly Gln Lys Arg Arg Leu Ser Phe Lys Pro
385 390 395 400

Gly Ile Thr Gly Leu Trp Gln Val Ser Gly Arg Ser Asn Ile Thr Asp
405 410 415

Phe Asp Asp Val Val Arg Leu Asp Leu Ala Tyr Ile Asp Asn Trp Thr
420 425 430

Ile Trp Ser Asp Ile Lys Ile Leu Leu Lys Thr Val Lys Val Val Leu
435 440 445

Leu Arg Glu Gly Ser Lys
450

<210> 31

<211> 149

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS1F

<400> 31

Met Lys Val Cys Leu Val Gly Ser Ser Gly Gly His Leu Thr His Leu
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Tyr Leu Leu Lys Pro Phe Trp Lys Glu Glu Glu Arg Phe Trp Val Thr
20 25 30

Phe Asp Lys Glu Asp Ala Arg Ser Leu Leu Lys Asn Glu Lys Met Tyr
35 40 45

Pro Cys Tyr Phe Pro Thr Asn Arg Asn Leu Ile Asn Leu Val Lys Asn
50 55 60

Thr Phe Leu Ala Phe Lys Ile Leu Arg Asp Glu Lys Pro Asp Val Ile
65 70 75 80

Ile Ser Ser Gly Ala Ala Val Ala Val Pro Phe Phe Tyr Ile Gly Lys
85 90 95

Leu Phe Gly Ala Lys Thr Ile Tyr Ile Glu Val Phe Asp Arg Val Asn
100 105 110

Lys Ser Thr Leu Thr Gly Lys Leu Val Tyr Pro Val Thr Asp Ile Phe
115 120 125

Ile Val Gln Trp Glu Glu Met Lys Lys Val Tyr Pro Lys Ser Ile Asn
130 135 140

Leu Gly Ser Ile Phe
145

<210> 32

<211> 164

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS1G

<400> 32

Met Ile Phe Val Thr Val Gly Thr His Glu Gln Gln Phe Asn Arg Leu
1 5 10 15

Ile Lys Glu Ile Asp Leu Leu Lys Lys Asn Gly Ser Ile Thr Asp Glu
20 25 30

Ile Phe Ile Gln Thr Gly Tyr Ser Asp Tyr Ile Pro Glu Tyr Cys Lys
35 40 45

Tyr Lys Lys Phe Leu Ser Tyr Lys Glu Met Glu Gln Tyr Ile Asn Lys
50 55 60

Ser Glu Val Val Ile Cys His Gly Gly Pro Ala Thr Phe Met Asn Ser
65 70 75 80

Leu Ser Lys Gly Lys Lys Gln Leu Leu Phe Pro Arg Gln Lys Lys Tyr
85 90 95

Gly Glu His Val Asn Asp His Gln Val Glu Phe Val Arg Arg Ile Leu
100 105 110

Gln Asp Asn Asn Ile Leu Phe Ile Glu Asn Ile Asp Asp Leu Phe Glu
115 120 125

Lys Ile Ile Glu Val Ser Lys Gln Thr Asn Phe Thr Ser Asn Asn Asn
130 135 140

Phe Phe Cys Glu Arg Leu Lys Gln Ile Val Glu Lys Phe Asn Glu Asp
145 150 155 160

Gln Glu Asn Glu

<210> 33

<211> 388

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS1H

<400> 33

Met Phe Lys Leu Phe Lys Tyr Asp Pro Glu Tyr Phe Ile Phe Lys Tyr
1 5 10 15

Phe Trp Leu Ile Ile Phe Ile Pro Glu Gln Lys Tyr Val Phe Leu Leu
20 25 30

Ile Phe Met Asn Leu Ile Leu Phe His Ile Lys Phe Leu Lys Thr Lys
35 40 45

Leu Ile Leu Lys Asn Glu Ile Leu Leu Phe Leu Leu Trp Ser Ile Leu
50 55 60

Cys Phe Val Ser Val Val Thr Ser Met Phe Val Glu Ile Asn Phe Glu
65 70 75 80

Arg Leu Phe Ala Asp Phe Thr Ala Pro Ile Ile Trp Ile Ile Ala Ile
85 90 95

Met Tyr Tyr Asn Leu Tyr Ser Phe Ile Asn Ile Asp Tyr Lys Lys Leu
100 105 110

Lys Asn Ser Ile Phe Phe Ser Phe Leu Val Leu Leu Gly Ile Ser Ala
115 120 125

Leu Tyr Ile Ile Gln Asn Gly Lys Asp Ile Val Phe Leu Asp Arg His
130 135 140

Leu Ile Gly Leu Asp Tyr Leu Ile Thr Gly Val Lys Thr Arg Leu Val
145 150 155 160

Gly Phe Met Asn Tyr Pro Thr Leu Asn Thr Thr Thr Ile Ile Val Ser
165 170 175

Ile Pro Leu Ile Phe Ala Leu Ile Lys Asn Lys Met Gln Gln Phe Phe
180 185 190

Phe Leu Cys Leu Ala Phe Ile Pro Ile Tyr Leu Ser Gly Ser Arg Ile
195 200 205

Gly Ser Leu Ser Leu Ala Ile Leu Ile Ile Cys Leu Leu Trp Arg Tyr
210 215 220

Ile Gly Gly Lys Phe Ala Trp Ile Lys Lys Leu Ile Val Ile Phe Val
225 230 235 240

Ile Leu Leu Ile Ile Leu Asn Thr Glu Leu Leu Tyr His Glu Ile Leu
245 250 255

Ala Val Tyr Asn Ser Arg Glu Ser Ser Asn Glu Ala Arg Phe Ile Ile
260 265 270

Tyr Gln Gly Ser Ile Asp Lys Val Leu Glu Asn Asn Ile Leu Phe Gly
275 280 285

Tyr Gly Ile Ser Glu Tyr Ser Val Thr Gly Thr Trp Leu Gly Ser His
290 295 300

Ser Gly Tyr Ile Ser Phe Phe Tyr Lys Ser Gly Ile Val Gly Leu Ile
305 310 315 320

Leu Leu Met Phe Ser Phe Phe Tyr Val Ile Lys Lys Ser Tyr Gly Val
325 330 335

Asn Gly Glu Thr Ala Leu Phe Tyr Phe Thr Ser Leu Ala Ile Phe Phe
340 345 350

Ile Tyr Glu Thr Ile Asp Pro Ile Ile Ile Ile Leu Val Leu Phe Phe
355 360 365

Ser Ser Ile Gly Ile Trp Asn Asn Ile Asn Phe Lys Lys Asp Met Glu
370 375 380

Thr Lys Asn Glu
385

<210> 34

<211> 322

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS1I

<400> 34

Met Asn Asp Leu Ile Ser Val Ile Val Pro Ile Tyr Asn Val Gln Asp
1 5 10 15

Tyr Leu Asp Lys Cys Ile Asn Ser Ile Ile Asn Gln Thr Tyr Thr Asn
20 25 30

Leu Glu Val Ile Leu Val Asn Asp Gly Ser Thr Asp Asp Ser Glu Lys
35 40 45

Ile Cys Leu Asn Tyr Met Lys Asn Asp Gly Arg Ile Lys Tyr Tyr Lys
50 55 60

Lys Ile Asn Gly Gly Leu Ala Asp Ala Arg Asn Phe Gly Leu Glu His
65 70 75 80

Ala Thr Gly Lys Tyr Ile Ala Phe Val Asp Ser Asp Asp Tyr Ile Glu
85 90 95

Val Ala Met Phe Glu Arg Met His Asp Asn Ile Thr Glu Tyr Asn Ala
100 105 110

Asp Ile Ala Glu Ile Asp Phe Cys Leu Val Asp Glu Asn Gly Tyr Thr
115 120 125

Lys Lys Lys Arg Asn Ser Asn Phe His Val Leu Thr Arg Glu Glu Thr
130 135 140

Val Lys Glu Phe Leu Ser Gly Ser Asn Ile Glu Asn Asn Val Trp Cys
145 150 155 160

Lys Leu Tyr Ser Arg Asp Ile Ile Lys Asp Ile Lys Phe Gln Ile Asn
165 170 175

Asn Arg Ser Ile Gly Glu Asp Leu Leu Phe Asn Leu Glu Val Leu Asn
180 185 190

Asn Val Thr Arg Val Val Val Asp Thr Arg Glu Tyr Tyr Tyr Asn Tyr
195 200 205

Val Ile Arg Asn Ser Ser Leu Ile Asn Gln Lys Phe Ser Ile Asn Asn
210 215 220

Ile Asp Leu Val Thr Arg Leu Glu Asn Tyr Pro Phe Lys Leu Lys Arg
225 230 235 240

Glu Phe Ser His Tyr Phe Asp Ala Lys Val Ile Lys Glu Lys Val Lys
245 250 255

Cys Leu Asn Lys Met Tyr Ser Thr Asp Cys Leu Asp Asn Glu Phe Leu
260 265 270

Pro Ile Leu Glu Ser Tyr Arg Lys Glu Ile Arg Arg Tyr Pro Phe Ile
275 280 285

Lys Ala Lys Arg Tyr Leu Ser Arg Lys His Leu Val Thr Leu Tyr Leu
290 295 300

Met Lys Phe Ser Pro Lys Leu Tyr Val Met Leu Tyr Lys Lys Phe Gln
305 310 315 320

Lys Gln

<210> 35

<211> 322

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS1J

<400> 35

Met Asp Lys Ile Ser Val Ile Val Pro Val Tyr Asn Val Asp Lys Tyr
1 5 10 15

Leu Ser Ser Cys Ile Glu Ser Ile Ile Asn Gln Asn Tyr Lys Asn Ile
20 25 30

Glu Ile Leu Leu Ile Asp Asp Gly Ser Val Asp Asp Ser Ala Lys Ile
35 40 45

Cys Lys Glu Tyr Glu Lys Asp Lys Arg Val Lys Ile Phe Phe Thr Asn
50 55 60

His Ser Gly Val Ser Asn Ala Arg Asn His Gly Ile Lys Arg Ser Thr
65 70 75 80

Ala Glu Tyr Ile Met Phe Val Asp Ser Asp Asp Val Val Asp Ser Arg
85 90 95

Leu Val Glu Lys Leu Tyr Phe Asn Ile Ile Lys Ser Arg Ser Asp Leu
100 105 110

Ser Gly Cys Leu Tyr Ala Thr Phe Ser Glu Asn Ile Asn Asn Phe Glu
115 120 125

Val Asn Asn Pro Asn Ile Asp Phe Glu Ala Ile Asn Thr Val Gln Asp
130 135 140

Met Gly Glu Lys Asn Phe Met Asn Leu Tyr Ile Asn Asn Ile Phe Ser
145 150 155 160

Thr Pro Val Cys Lys Leu Tyr Lys Lys Arg Tyr Ile Thr Asp Leu Phe
165 170 175

Gln Glu Asn Gln Trp Leu Gly Glu Asp Leu Leu Phe Asn Leu His Tyr
180 185 190

Leu Lys Asn Ile Asp Arg Val Ser Tyr Leu Thr Glu His Leu Tyr Phe
195 200 205

Tyr Arg Arg Gly Ile Leu Ser Thr Val Asn Ser Phe Lys Glu Gly Val
210 215 220

Phe Leu Gln Leu Glu Asn Leu Gln Lys Gln Val Ile Val Leu Phe Lys
225 230 235 240

Gln Ile Tyr Gly Glu Asp Phe Asp Val Ser Ile Val Lys Asp Thr Ile
245 250 255

Arg Trp Gln Val Phe Tyr Tyr Ser Leu Leu Met Phe Lys Tyr Gly Lys
260 265 270

Gln Ser Ile Phe Asp Lys Phe Leu Ile Phe Arg Asn Leu Tyr Lys Lys
275 280 285

Tyr Tyr Phe Asn Leu Leu Lys Val Ser Asn Lys Asn Ser Leu Ser Lys
290 295 300

Asn Phe Cys Ile Arg Ile Val Ser Asn Lys Val Phe Lys Lys Ile Leu
305 310 315 320

Trp Leu

<210> 36

<211> 278

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS1K

<400> 36

Met Asp Thr Ile Ser Lys Ile Ser Ile Ile Val Pro Ile Tyr Asn Val
1 5 10 15

Glu Lys Tyr Leu Ser Lys Cys Ile Asp Ser Ile Val Asn Gln Thr Tyr
20 25 30

Lys His Ile Glu Ile Leu Leu Val Asn Asp Gly Ser Thr Asp Asn Ser
35 40 45

Glu Glu Ile Cys Leu Ala Tyr Ala Lys Lys Asp Ser Arg Ile Arg Tyr
50 55 60

Phe Lys Lys Glu Asn Gly Gly Leu Ser Asp Ala Arg Asn Tyr Gly Ile
65 70 75 80

Ser Arg Ala Lys Gly Asp Tyr Leu Ala Phe Ile Asp Ser Asp Asp Phe
85 90 95

Ile His Ser Glu Phe Ile Gln Arg Leu His Glu Ala Ile Glu Arg Glu
100 105 110

Asn Ala Leu Val Ala Val Ala Gly Tyr Asp Arg Val Asp Ala Ser Gly
115 120 125

His Phe Leu Thr Ala Glu Pro Leu Pro Thr Asn Gln Ala Val Leu Ser
130 135 140

Gly Arg Asn Val Cys Lys Lys Leu Leu Glu Ala Asp Gly His Arg Phe
145 150 155 160

Val Val Ala Cys Asn Lys Leu Tyr Lys Lys Glu Leu Phe Glu Asp Phe
165 170 175

Arg Phe Glu Lys Gly Lys Ile His Glu Asp Glu Tyr Phe Thr Tyr Arg
180 185 190

Leu Leu Tyr Glu Leu Glu Lys Val Ala Ile Val Lys Glu Cys Leu Tyr
195 200 205

Tyr Tyr Val Asp Arg Glu Asn Ser Ile Thr Thr Ser Ser Met Thr Asp
210 215 220

His Arg Phe His Cys Leu Leu Glu Phe Gln Asn Glu Arg Met Asp Phe
225 230 235 240

Tyr Glu Ser Arg Gly Asp Lys Glu Leu Leu Leu Glu Cys Tyr Arg Ser
245 250 255

Phe Leu Ala Phe Ala Val Leu Phe Leu Gly Lys Tyr Asn His Trp Leu
260 265 270

Ser Lys Gln Gln Lys Lys
275

<210> 37

<211> 4519

<212> DNA

<213> Streptococcus suis

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<223> CPS9

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taagcaaact tgaaaaaaag aaagtaccca cacttaatgg ctcgcgctat attcttttgg 240

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tgggatgttc aataggaggg ggaacagaga acaaattaac agttggacat tactaattga 3960

atttatgtta gctcaaggaa ttgttacacc actagatgta tttattaatc aaatttacat 4020

tagggtcttt gtttatatgc caacttggat aaagaaactc atttatggaa aaatcttaag 4080

gaaatagtat gattacagta ttgatggcta catataatgg aagcccattt ataataaaac 4140

agttagattc aattcgaaat caaagtgtat cagcagacaa agttattatt tgggatgatt 4200

gctcgacaga tgatacaata aaaataataa aagattatat aaaaaaatat tctttggatt 4260

catgggttgt ctctcaaaat aaatctaatc aggggcatta tcaaacattt ataaatttga 4320

caaagttagt tcaggaagga atagtctttt tttcagatca agatgatatt tgggactgtc 4380

ataaaattga gacaatgctt ccaatctttg acagagaaaa tgtatcaatg gtgttttgca 4440

aatccagatt gattgatgaa aacggaaata ttatcagtag cccagatact tcggatagaa 4500

tcaatacgta ctctctaga 4519

<210> 38

<211> 215

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS9D

<400> 38

Ala Tyr Arg Gln Gly Val Arg Tyr Ile Val Ala Thr Ser His Arg Arg
1 5 10 15

Lys Gly Met Phe Glu Thr Pro Glu Lys Val Ile Met Thr Asn Phe Leu
20 25 30

Gln Phe Lys Asp Ala Val Ala Glu Val Tyr Pro Glu Ile Arg Leu Cys
35 40 45

Tyr Gly Ala Glu Leu Tyr Tyr Ser Lys Asp Ile Leu Ser Lys Leu Glu
50 55 60

Lys Lys Lys Val Pro Thr Leu Asn Gly Ser Arg Tyr Ile Leu Leu Glu
65 70 75 80

Phe Ser Ser Asp Thr Pro Trp Lys Glu Ile Gln Glu Ala Val Asn Glu
85 90 95

Val Thr Leu Leu Gly Leu Thr Pro Val Leu Ala His Ile Glu Arg Tyr
100 105 110

Asp Ala Leu Ala Phe His Ala Glu Arg Val Glu Glu Leu Ile Asp Lys
115 120 125

Gly Cys Tyr Thr Gln Val Asn Ser Asn His Val Leu Lys Pro Thr Leu
130 135 140

Ile Gly Asp Arg Ala Lys Glu Phe Lys Lys Arg Thr Arg Tyr Phe Leu
145 150 155 160

Glu Gln Asp Leu Val His Cys Val Ala Ser Asp Met His Asn Leu Ser
165 170 175

Ser Arg Pro Pro Phe Met Arg Glu Ala Tyr Lys Leu Leu Thr Glu Glu
180 185 190

Phe Gly Lys Asp Lys Ala Lys Ala Leu Leu Lys Lys Asn Pro Leu Met
195 200 205

Leu Leu Lys Asn Gln Ala Ile
210 215

<210> 39

<211> 608

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS9E

<400> 39

Met Asp Leu Gly Thr Val Thr Asp Lys Leu Leu Glu Arg Asn Ser Lys
1 5 10 15

Arg Leu Ile Leu Val Cys Met Asp Thr Cys Leu Leu Ile Val Ser Met
20 25 30

Ile Leu Ser Arg Leu Phe Leu Asp Val Ile Ile Asp Ile Pro Asp Glu
35 40 45

Arg Phe Ile Leu Ala Val Leu Phe Val Ser Ile Leu Tyr Leu Ile Leu
50 55 60

Ser Phe Arg Leu Lys Val Phe Ser Leu Ile Thr Arg Tyr Thr Gly Tyr
65 70 75 80

Gln Ser Tyr Val Lys Ile Gly Leu Ser Leu Ile Ser Ala His Ser Leu
85 90 95

Phe Leu Ile Ile Ser Met Val Leu Trp Gln Ala Phe Ser Tyr Arg Phe
100 105 110

Ile Leu Val Ser Leu Phe Leu Ser Tyr Val Met Leu Ile Thr Pro Arg
115 120 125

Ile Val Trp Lys Val Leu His Glu Thr Arg Lys Asn Ala Ile Arg Lys
130 135 140

Lys Asp Ser Pro Leu Arg Ile Leu Val Val Gly Ala Gly Asp Gly Gly
145 150 155 160

Asn Ile Phe Ile Asn Thr Val Lys Asp Arg Lys Leu Asn Phe Glu Ile
165 170 175

Val Gly Ile Val Asp Arg Asp Pro Asn Lys Leu Gly Thr Phe Ile Arg
180 185 190

Thr Ala Lys Val Leu Gly Asn Arg Asn Asp Ile Pro Arg Leu Val Glu
195 200 205

Glu Leu Ala Val Asp Gln Val Thr Ile Ala Ile Pro Ser Leu Asn Gly
210 215 220

Lys Glu Arg Glu Lys Ile Val Glu Ile Cys Asn Thr Thr Gly Val Thr
225 230 235 240

Val Asn Asn Met Pro Ser Ile Glu Asp Ile Met Ala Gly Asn Met Ser
245 250 255

Val Ser Ala Phe Gln Glu Ile Asp Val Ala Asp Leu Leu Gly Arg Pro
260 265 270

Glu Val Val Leu Asp Gln Asp Glu Leu Asn Gln Phe Phe Gln Gly Lys
275 280 285

Thr Ile Leu Val Thr Gly Ala Gly Gly Ser Ile Gly Ser Glu Leu Cys
290 295 300

Arg Gln Ile Ala Lys Phe Thr Pro Lys Arg Leu Leu Leu Leu Gly His
305 310 315 320

Gly Glu Asn Ser Ile Tyr Leu Ile His Arg Glu Leu Leu Glu Lys Tyr
325 330 335

Gln Gly Lys Ile Glu Leu Val Pro Leu Ile Ala Asp Ile Gln Asp Arg
340 345 350

Glu Leu Ile Phe Ser Ile Met Ala Glu Tyr Gln Pro Asp Val Val Tyr
355 360 365

His Ala Ala Ala His Lys His Val Pro Leu Met Glu Tyr Asn Pro His
370 375 380

Glu Ala Val Lys Asn Asn Ile Phe Gly Thr Lys Asn Val Ala Glu Ala
385 390 395 400

Ala Lys Thr Ala Lys Val Ala Lys Phe Val Met Val Ser Thr Asp Lys
405 410 415

Ala Val Asn Pro Pro Asn Val Met Gly Ala Thr Lys Arg Val Ala Glu
420 425 430

Met Ile Val Thr Gly Leu Asn Glu Pro Gly Gln Thr Gln Phe Ala Ala
435 440 445

Val Arg Phe Gly Asn Val Leu Gly Ser Arg Gly Ser Val Val Pro Leu
450 455 460

Phe Lys Glu Gln Ile Arg Lys Gly Gly Pro Val Thr Val Thr Asp Phe
465 470 475 480

Arg Met Thr Arg Tyr Phe Met Thr Ile Pro Glu Ala Ser Arg Leu Val
485 490 495

Ile Gln Ala Gly His Leu Ala Lys Gly Gly Glu Ile Phe Val Leu Asp
500 505 510

Met Gly Glu Pro Val Gln Ile Leu Glu Leu Ala Arg Lys Val Ile Leu
515 520 525

Leu Ser Gly His Thr Glu Glu Glu Ile Gly Ile Val Glu Ser Gly Ile
530 535 540

Arg Pro Gly Glu Lys Leu Tyr Glu Glu Leu Leu Ser Thr Glu Glu Arg
545 550 555 560

Val Ser Glu Gln Ile His Glu Lys Ile Phe Val Gly Arg Val Thr Asn
565 570 575

Lys Gln Ser Asp Ile Val Asn Ser Phe Ile Asn Gly Leu Leu Gln Lys
580 585 590

Asp Arg Asn Glu Leu Lys Asn Met Leu Ile Glu Phe Ala Lys Gln Glu
595 600 605

<210> 40

<211> 200

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS9F

<400> 40

Met Tyr Pro Ile Cys Lys Arg Ile Leu Ala Ile Ile Ile Ser Gly Ile
1 5 10 15

Ala Ile Val Val Leu Ser Pro Ile Leu Leu Leu Ile Ala Leu Ala Ile
20 25 30

Lys Leu Asp Ser Lys Gly Pro Val Leu Phe Lys Gln Lys Arg Val Gly
35 40 45

Lys Asn Lys Ser Tyr Phe Met Ile Tyr Lys Phe Arg Ser Met Tyr Val
50 55 60

Asp Ala Pro Ser Asp Met Pro Thr His Leu Leu Lys Asp Pro Lys Ala
65 70 75 80

Met Ile Thr Lys Val Gly Ala Phe Leu Arg Lys Thr Ser Leu Asp Glu
85 90 95

Leu Pro Gln Leu Phe Asn Ile Phe Lys Gly Glu Met Ala Ile Val Gly
100 105 110

Pro Arg Pro Ala Leu Trp Asn Gln Tyr Asp Leu Ile Glu Glu Arg Asp
115 120 125

Lys Tyr Gly Ala Asn Asp Ile Arg Pro Gly Leu Thr Gly Trp Ala Gln
130 135 140

Ile Asn Gly Arg Asp Glu Leu Glu Ile Asp Glu Lys Ser Lys Leu Asp
145 150 155 160

Gly Tyr Tyr Val Gln Asn Met Ser Leu Gly Leu Asp Ile Lys Cys Phe
165 170 175

Leu Gly Thr Phe Leu Ser Val Ala Arg Ser Glu Gly Val Val Glu Gly
180 185 190

Gly Thr Gly Gln Lys Gly Lys Gly
195 200

<210> 41

<211> 269

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS2G

<400> 41

Met Lys Phe Ser Val Leu Met Ser Val Tyr Glu Lys Glu Lys Pro Glu
1 5 10 15

Phe Leu Arg Glu Ser Leu Glu Ser Ile Leu Val Asn Gln Thr Met Ile
20 25 30

Pro Thr Glu Val Val Leu Val Glu Asp Gly Pro Leu Asn Gln Ser Leu
35 40 45

Tyr Ser Ile Leu Glu Glu Phe Lys Ser Arg Phe Ser Phe Phe Lys Thr
50 55 60

Ile Ala Leu Glu Lys Asn Ser Gly Leu Gly Ile Ala Leu Asn Glu Gly
65 70 75 80

Leu Lys His Cys Asn Tyr Glu Trp Val Cys Thr Lys Trp Ile Leu Met
85 90 95

Met Leu His Ile His Thr Arg Phe Glu Lys Gln Val Asn Phe Ile Lys
100 105 110

Gln Asn Pro Thr Ile Asp Ile Glu Ile Asp Glu Phe Leu Asn Ser Thr
115 120 125

Ser Glu Ile Val Ser His Lys Asn Val Pro Thr Gln His Asp Glu Ile
130 135 140

Leu Lys Met Ala Arg Arg Glu Lys Ser Met Cys His Met Thr Val Met
145 150 155 160

Phe Lys Lys Lys Ser Val Glu Arg Ala Gly Gly Tyr Gln Thr Leu Pro
165 170 175

Tyr Val Glu Asp Tyr Phe Leu Trp Val Arg Met Ile Ala Ser Gly Ser
180 185 190

Lys Phe Ala Asn Ile Asp Glu Thr Leu Val Leu Ala Arg Val Gly Asn
195 200 205

Gly Met Phe Asn Arg Arg Gly Asn Arg Glu Gln Ile Asn Ser Trp Thr
210 215 220

Leu Leu Ile Glu Phe Met Leu Ala Gln Gly Ile Val Thr Pro Leu Asp
225 230 235 240

Val Phe Ile Asn Gln Ile Tyr Ile Arg Val Phe Val Tyr Met Pro Thr
245 250 255

Trp Ile Lys Lys Leu Ile Tyr Gly Lys Ile Leu Arg Lys
260 265

<210> 42

<211> 143

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS9H

<400> 42

Met Ile Thr Val Leu Met Ala Thr Tyr Asn Gly Ser Pro Phe Ile Ile
1 5 10 15

Lys Gln Leu Asp Ser Ile Arg Asn Gln Ser Val Ser Ala Asp Lys Val
20 25 30

Ile Ile Trp Asp Asp Cys Ser Thr Asp Asp Thr Ile Lys Ile Ile Lys
35 40 45

Asp Tyr Ile Lys Lys Tyr Ser Leu Asp Ser Trp Val Val Ser Gln Asn
50 55 60

Lys Ser Asn Gln Gly His Tyr Gln Thr Phe Ile Asn Leu Thr Lys Leu
65 70 75 80

Val Gln Glu Gly Ile Val Phe Phe Ser Asp Gln Asp Asp Ile Trp Asp
85 90 95

Cys His Lys Ile Glu Thr Met Leu Pro Ile Phe Asp Arg Glu Asn Val
100 105 110

Ser Met Val Phe Cys Lys Ser Arg Leu Ile Asp Glu Asn Gly Asn Ile
115 120 125

Ile Ser Ser Pro Asp Thr Ser Asp Arg Ile Asn Thr Tyr Ser Leu
130 135 140

<210> 43

<211> 3738

<212> DNA

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS7

<400> 43

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atatttttgg aacgaagaat gtggctgagg cggctaaaac tgcaaaggtt gccaaatttg 120

ttatggtttc aacagataaa gctgttaatc cgccaaatgt catgggagcg actaaacgtg 180

ttgcagaaat gattgtaaca ggtttaaacg agccaggtca gactcaattt gcggcagtcc 240

gttttgggaa tgttctaggt agtcgtggaa gtgttgttcc gctattcaaa gagcaaatta 300

gaaaaggtgg acctgttacg gttaccgact ttaggatgac tcgttatttc atgacgattc 360

ctgaggcaag tcgtttggtt atccaagctg gacatttggc aaaaggtgga gaaatctttg 420

tcttggatat gggtgagcca gtacaaatcc tggaattggc aagaaaagtt atcttgttaa 480

gcggacatac agaggaagaa atcgggattg tagaatctgg aatcagacca ggcgagaaac 540

tctacgagga attgttatca acagaagaac gtgtcagcga acagattcat gaaaaaatat 600

ttgtgggtcg cgttacaaat aagcagtcgg acattgtcaa ttcatttatc aatggattac 660

tccaaaaaga tagaaatgaa ttaaaagata tgttgattga atttgcaaaa caagaataag 720

aaagtaaaaa atatttttac tttcctagag tttaaacgat gtttaagttc taggaaggtt 780

ggaattgctt tcgtggaggt gatagataga aacctatata tttgtagaag aaaggatatt 840

aaactaaagg tgaatcggaa cataaagttt agatagagtt ggtatttaat gccaaacagg 900

tgaatgcaac ctctcgctcg ttactaagca ggagatagta aagttgcttg aaagagagtt 960

tgttaatcag tataagtagg ctaaagtgag aatatatatc tattattatc ggtaatgata 1020

ctattattga gaattattgt agtggggata aaaataattt ttggtgattt tatcgtccga 1080

cttaaaggtg ggttaaaaaa gtacttatat tcttttagaa ttgatgaaaa atatgggggga 1140

atataatatt tataggagat acgatgacta gagtagagtt gattactaga gaatttttta 1200

agaagaatga agcaaccagt aaatattttc agaagataga atcaagaaga ggtgaattat 1260

ttattaaatt ctttatggat aagttacttg cgcttatcct attattgcta ttatccccag 1320

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aagaacgtgt tacgagatat ggtcgaattt ttagaatatt taagtttaga acaatgattt 1440

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tcggtcacat tatcagaaaa tatcggctgg acgaagtgcc ccaacttttt aatgttttaa 1560

tgggggatat gagctttgta ggtgtaagac cagaagtaca aaaatatgta aatcagtata 1620

ctgatgaaat gtttgcgacg ttacttttac ctgcaggaat tacttcacca gcgagtattg 1680

catataagga tgaagatatt gttttagaag aatattgttc tcaaggctat agtcctgatg 1740

aagcatatgt tcaaaaagta ttaccagaaa aaatgaagta caatttggaa tatatcagaa 1800

actttggaat tatttctgat tttaaagtaa tgattgatac agtaattaaa gtaataaaat 1860

aggagattaa aatgacaaaa agacaaaata ttccattttc accaccagat attacccaag 1920

ctgaaattga tgaagttatt gacacactaa aatctggttg gattacaaca ggaccaaaga 1980

caaaagagct agaacgtcgg ctatcagtat ttacaggaac caataaaact gtgtgtttaa 2040

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aagttattgt tcctgctatg acctatactg cctcatgtag tgtcattact catgtaggag 2160

caactcctgt gatggttgat attcaaaaaa acagctttga gatggaatat gatgctttgg 2220

aaaaagcgat tactccgaaa acaaaagtta tcattcctgt tgatctagct ggtattcctt 2280

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ataataaatg gcagaaactt tttgggcgag ttattatcct atctgatagt gcacactcac 2400

taggtgctag ttataaggga aaaccagcgg gttccctagc agattttacc tcattttctt 2460

tccatgcagt taagaatttt acaactgctg aaggaggtag tgtgacatgg agatcacatc 2520

ctgatttgga tgacgaagag atgtataaag agtttcagat ttactctctt catggtcaga 2580

caaaggatgc attagctaag acacaattag ggtcatggga atatgacatt gttattcctg 2640

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aaagtttttt aaaaattcga ataatttagg ggcagctcta acacgaaata aggcactaag 3360

aaaagctaga ggtaggtgga ttgcgttctt ggattcagat gatttatggc acccgagtaa 3420

gctagaaaaa cagcttgaat ttatgaaaaa taatggatat tcatttactt atcacaattt 3480

tgaaaagatt gatgaatcta gtcagtcttt acgtgtcctg gtgtcaggac cagcaattgt 3540

gactagaaaa atgatgtaca attacggcta tccagggtgt ttgactttca tgtatgatgc 3600

agacaaaatg ggtttaattc agataaaaga tataaagaaa aataacgatt atgcgatatt 3660

acttcaattg tgtaagaagt atgactgtta tcttttaaat gaaagtttag cttcgtatcg 3720

aattagaaaa aaatcgat 3738

<210> 44

<211> 238

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS7E

<400> 44

Ala Ala His Lys His Val Pro Leu Met Glu Tyr Asn Pro His Glu Ala
1 5 10 15

Val Lys Asn Asn Ile Phe Gly Thr Lys Asn Val Ala Glu Ala Ala Lys
20 25 30

Thr Ala Lys Val Ala Lys Phe Val Met Val Ser Thr Asp Lys Ala Val
35 40 45

Asn Pro Pro Asn Val Met Gly Ala Thr Lys Arg Val Ala Glu Met Ile
50 55 60

Val Thr Gly Leu Asn Glu Pro Gly Gln Thr Gln Phe Ala Ala Val Arg
65 70 75 80

Phe Gly Asn Val Leu Gly Ser Arg Gly Ser Val Val Pro Leu Phe Lys
85 90 95

Glu Gln Ile Arg Lys Gly Gly Pro Val Thr Val Thr Asp Phe Arg Met
100 105 110

Thr Arg Tyr Phe Met Thr Ile Pro Glu Ala Ser Arg Leu Val Ile Gln
115 120 125

Ala Gly His Leu Ala Lys Gly Gly Glu Ile Phe Val Leu Asp Met Gly
130 135 140

Glu Pro Val Gln Ile Leu Glu Leu Ala Arg Lys Val Ile Leu Leu Ser
145 150 155 160

Gly His Thr Glu Glu Glu Ile Gly Ile Val Glu Ser Gly Ile Arg Pro
165 170 175

Gly Glu Lys Leu Tyr Glu Glu Leu Leu Ser Thr Glu Glu Arg Val Ser
180 185 190

Glu Gln Ile His Glu Lys Ile Phe Val Gly Arg Val Thr Asn Lys Gln
195 200 205

Ser Asp Ile Val Asn Ser Phe Ile Asn Gly Leu Leu Gln Lys Asp Arg
210 215 220

Asn Glu Leu Lys Asp Met Leu Ile Glu Phe Ala Lys Gln Glu
225 230 235

<210> 45

<211> 232

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS7F

<400> 45

Met Thr Arg Val Glu Leu Ile Thr Arg Glu Phe Phe Lys Lys Asn Glu
1 5 10 15

Ala Thr Ser Lys Tyr Phe Gln Lys Ile Glu Ser Arg Arg Gly Glu Leu
20 25 30

Phe Ile Lys Phe Phe Met Asp Lys Leu Leu Ala Leu Ile Leu Leu Leu
35 40 45

Leu Leu Ser Pro Val Ile Ile Ile Leu Ala Ile Trp Ile Lys Leu Asp
50 55 60

Ser Lys Gly Pro Ile Phe Tyr Arg Gln Glu Arg Val Thr Arg Tyr Gly
65 70 75 80

Arg Ile Phe Arg Ile Phe Lys Phe Arg Thr Met Ile Ser Asp Ala Asp
85 90 95

Lys Val Gly Ser Leu Val Thr Val Gly Gln Asp Asn Arg Ile Thr Lys
100 105 110

Val Gly His Ile Ile Arg Lys Tyr Arg Leu Asp Glu Val Pro Gln Leu
115 120 125

Phe Asn Val Leu Met Gly Asp Met Ser Phe Val Gly Val Arg Pro Glu
130 135 140

Val Gln Lys Tyr Val Asn Gln Tyr Thr Asp Glu Met Phe Ala Thr Leu
145 150 155 160

Leu Leu Pro Ala Gly Ile Thr Ser Pro Ala Ser Ile Ala Tyr Lys Asp
165 170 175

Glu Asp Ile Val Leu Glu Glu Tyr Cys Ser Gln Gly Tyr Ser Pro Asp
180 185 190

Glu Ala Tyr Val Gln Lys Val Leu Pro Glu Lys Met Lys Tyr Asn Leu
195 200 205

Glu Tyr Ile Arg Asn Phe Gly Ile Ile Ser Asp Phe Lys Val Met Ile
210 215 220

Asp Thr Val Ile Lys Val Ile Lys
225 230

<210> 46

<211> 404

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS7G

<400> 46

Met Thr Lys Arg Gln Asn Ile Pro Phe Ser Pro Pro Asp Ile Thr Gln
1 5 10 15

Ala Glu Ile Asp Glu Val Ile Asp Thr Leu Lys Ser Gly Trp Ile Thr
20 25 30

Thr Gly Pro Lys Thr Lys Glu Leu Glu Arg Arg Leu Ser Val Phe Thr
35 40 45

Gly Thr Asn Lys Thr Val Cys Leu Asn Ser Ala Thr Ala Gly Leu Glu
50 55 60

Leu Val Leu Arg Ile Leu Gly Val Gly Pro Gly Asp Glu Val Ile Val
65 70 75 80

Pro Ala Met Thr Tyr Thr Ala Ser Cys Ser Val Ile Thr His Val Gly
85 90 95

Ala Thr Pro Val Met Val Asp Ile Gln Lys Asn Ser Phe Glu Met Glu
100 105 110

Tyr Asp Ala Leu Glu Lys Ala Ile Thr Pro Lys Thr Lys Val Ile Ile
115 120 125

Pro Val Asp Leu Ala Gly Ile Pro Cys Asp Tyr Asp Lys Ile Tyr Thr
130 135 140

Ile Val Glu Asn Lys Arg Ser Leu Tyr Val Ala Ser Asp Asn Lys Trp
145 150 155 160

Gln Lys Leu Phe Gly Arg Val Ile Ile Leu Ser Asp Ser Ala His Ser
165 170 175

Leu Gly Ala Ser Tyr Lys Gly Lys Pro Ala Gly Ser Leu Ala Asp Phe
180 185 190

Thr Ser Phe Ser Phe His Ala Val Lys Asn Phe Thr Thr Ala Glu Gly
195 200 205

Gly Ser Val Thr Trp Arg Ser His Pro Asp Leu Asp Asp Glu Glu Met
210 215 220

Tyr Lys Glu Phe Gln Ile Tyr Ser Leu His Gly Gln Thr Lys Asp Ala
225 230 235 240

Leu Ala Lys Thr Gln Leu Gly Ser Trp Glu Tyr Asp Ile Val Ile Pro
245 250 255

Gly Tyr Lys Cys Asn Met Thr Asp Ile Met Ala Gly Ile Gly Leu Val
260 265 270

Gln Leu Glu Arg Tyr Pro Ser Leu Leu Asn Arg Arg Arg Glu Ile Ile
275 280 285

Glu Lys Tyr Asn Ala Gly Phe Glu Gly Thr Ser Ile Lys Pro Leu Val
290 295 300

His Leu Thr Glu Asp Lys Gln Ser Ser Met His Leu Tyr Ile Thr His
305 310 315 320

Leu Gln Gly Tyr Thr Leu Glu Gln Arg Asn Glu Val Ile Gln Lys Met
325 330 335

Ala Glu Ala Gly Ile Ala Cys Asn Val His Tyr Lys Pro Leu Pro Leu
340 345 350

Leu Thr Ala Tyr Lys Asn Leu Gly Phe Glu Met Lys Asp Phe Pro Asn
355 360 365

Ala Tyr Gln Tyr Phe Glu Asn Glu Val Thr Leu Pro Leu His Thr Asn
370 375 380

Leu Ser Asp Glu Asp Val Glu Tyr Val Ile Glu Met Phe Leu Lys Ile
385 390 395 400

Val Ser Arg Asp

<210> 47

<211> 210

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> CPS7H

<400> 47

Met Val Glu Arg Asp Met Val Glu Arg Asp Thr Leu Val Ser Ile Ile
1 5 10 15

Met Pro Ser Trp Asn Thr Ala Lys Tyr Ile Ser Glu Ser Ile Gln Ser
20 25 30

Val Leu Asp Gln Thr His Gln Asn Trp Glu Leu Ile Ile Val Asp Asp
35 40 45

Cys Ser Asn Asp Glu Thr Glu Lys Val Val Ser His Phe Lys Asp Ser
50 55 60

Arg Ile Lys Phe Phe Lys Asn Ser Asn Asn Leu Gly Ala Ala Leu Thr
65 70 75 80

Arg Asn Lys Ala Leu Arg Lys Ala Arg Gly Arg Trp Ile Ala Phe Leu
85 90 95

Asp Ser Asp Asp Leu Trp His Pro Ser Lys Leu Glu Lys Gln Leu Glu
100 105 110

Phe Met Lys Asn Asn Gly Tyr Ser Phe Thr Tyr His Asn Phe Glu Lys
115 120 125

Ile Asp Glu Ser Ser Gln Ser Leu Arg Val Leu Val Ser Gly Pro Ala
130 135 140

Ile Val Thr Arg Lys Met Met Tyr Asn Tyr Gly Tyr Pro Gly Cys Leu
145 150 155 160

Thr Phe Met Tyr Asp Ala Asp Lys Met Gly Leu Ile Gln Ile Lys Asp
165 170 175

Ile Lys Lys Asn Asn Asp Tyr Ala Ile Leu Leu Gln Leu Cys Lys Lys
180 185 190

Tyr Asp Cys Tyr Leu Leu Asn Glu Ser Leu Ala Ser Tyr Arg Ile Arg
195 200 205

Lys Lys
210

<210> 48

<211> 101

<212> DNA

<213> Streptococcus suis

<220>

<221> misc_feature

<222> (1)..(101)

<223> N may be any nucleotide

<220>

<221> misc_feature

<223> 100 base pair repeat between CPS2G and CPS2H

<400> 48

aagggcacct ctataaactc ccaaaattgc gaatttggag ttacgaaagc cttgttaaat 60

caancatttt aaattttaga aaattagttt ttagagctcc c 101

<210> 49

<211> 101

<212> DNA

<213> Streptococcus suis

<220>

<221> misc_feature

<222> (1)..(101)

<223> N may be any nucleotide

<220>

<221> misc_feature

<223> 100 base pair repeat within CPS2M

<400> 49

ggcgccacct ctataaattc ccaaaattgc gaatttcgag ttacgaaagc cttgttaaat 60

caancatctt aaattttaga aaattagttt ttagaggtcc c 101

<210> 50

<211> 101

<212> DNA

<213> Streptococcus suis

<220>

<221> misc_feature

<223> 100 base pair repeat between CPS2O and CPS2P

<400> 50

aagggcacct ctataaactc ccaaaattgc gaatttcgag ttacgaaagc cttgttaaat 60

caaacatttt aaattttaga aaattagttt ttagaggtcc c 101

<210> 51

<211> 120

<212> PRT

<213> Streptococcus suis

<220>

<221> misc_feature

<223> N-terminal part of CPS2J

<400> 51

Met Ala Lys Val Ser Ile Ile Val Pro Ile Phe Asn Thr Glu Lys Tyr
1 5 10 15

Leu Arg Glu Cys Leu Asp Ser Ile Ile Ser Gln Ser Tyr Thr Asn Leu
20 25 30

Glu Ile Leu Leu Ile Asp Asp Gly Ser Ser Asp Ser Ser Thr Asp Ile
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Cys Leu Glu Tyr Ala Glu Gln Asp Gly Arg Ile Lys Leu Phe Arg Leu
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Tyr Ile Leu Glu Asp Arg Asp Phe Gln Asp His Thr Cys Arg Ala Gln
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Ser Tyr Arg Leu Ser Arg Ile Thr Tyr Glu Asp Phe Arg Ile Cys Leu
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Lys Glu Ser Leu Ile Gly Arg Glu Asn Tyr Leu Phe Asn Tyr Tyr His
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Gln Gln Glu Gly Leu Ala Glu Leu Ile Ser Ser Val Gln Ser Leu Leu
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Met Asp Tyr His Val Tyr Thr Lys Lys Asp Gln Leu Val Ile Thr Ala
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Gly Ser Gln Gln Ala Leu Tyr Ile Leu Thr Gln Met Glu Thr Leu Ala
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CLAIMS

What is claimed is:

1. An isolated or recombinant nucleic acid encoding a capsular gene cluster of *Streptococcus suis* or a gene or gene fragment derived thereof.

2. The isolated or recombinant nucleic acid of claim 1, wherein said nucleic acid encodes a *Streptococcus suis* serotype-specific central region.

3. The isolated or recombinant nucleic acid of claim 1 or claim 2, wherein said isolated or recombinant nucleic acid is hybridized to a second nucleic acid encoding a gene derived from a *Streptococcus suis* serotype 1, 2, or 9 capsular gene cluster.

4. An isolated or recombinant nucleic acid encoding a capsular gene cluster of *Streptococcus suis* serotype 2 or a gene or gene fragment derived thereof, wherein said isolated or recombinant nucleic acid comprises SEQ. ID. NO. 9 and said isolated or recombinant nucleic acid encodes a capsular gene cluster of *Streptococcus suis* serotype 2 or a gene or gene fragment derived thereof selected from the group of sequences consisting of SEQ. ID. NO. 10, SEQ. ID. NO. 53, SEQ. ID. NO.11, SEQ. ID. NO.12, SEQ. ID. NO.13, SEQ. ID. NO.14, SEQ. ID. NO.15, SEQ. ID. NO.16, SEQ. ID. NO.17, SEQ. ID. NO.18, SEQ. ID. NO.19, SEQ. ID. NO.20, SEQ. ID. NO.21, SEQ. ID. NO.22, SEQ. ID. NO.23, SEQ. ID. NO.24, SEQ. ID. NO.25, SEQ. ID. NO. 26, SEQ. ID. NO.27 and SEQ. ID. NO. 28.

5. An isolated or recombinant nucleic acid encoding a capsular gene cluster of *Streptococcus suis* serotype 1 or a gene or gene fragment derived thereof, wherein said isolated or recombinant nucleic acid is SEQ. ID. NO.29 and said isolated or recombinant nucleic acid encodes a capsular gene cluster of *Streptococcus suis* serotype 1 or a gene or gene fragment derived thereof selected from the group consisting of SEQ. ID. NO.30, SEQ. ID. NO. 31, SEQ. ID. NO.32, SEQ. ID. NO.33, SEQ. ID. NO.34, SEQ. ID. NO.35 and SEQ. ID. NO.36.

6. An isolated or recombinant nucleic acid encoding a capsular gene cluster of *Streptococcus suis* serotype 9 or a gene or gene fragment derived thereof, wherein said nucleic acid comprises SEQ. ID. NO.37 and wherein said isolated or recombinant nucleic acid encodes a capsular gene cluster of *Streptococcus suis* serotype 9 or a gene or gene fragment derived thereof selected from the group consisting of SEQ. ID. NO.38, SEQ. ID. NO.39, SEQ. ID. NO.40, SEQ. ID. NO.41, and SEQ. ID. NO.42.

7. A nucleic acid probe or primer derived from the isolated or recombinant nucleic acid of any one of claims 1 to 6, wherein said nucleic acid probe or primer allows species or serotype specific detection of *Streptococcus suis*.

8. The nucleic acid probe or primer of claim 7, wherein said nucleic acid probe or primer further comprises at least one reporter molecule.

9. A diagnostic test kit comprising the nucleic acid probe or primer of claim 7 or claim 8.

10. A protein or fragment thereof encoded by the isolated or recombinant nucleic acid of any one of claims 1 to 6.

11. The protein or fragment of claim 10, wherein said protein or fragment is capable of polysaccharide biosynthesis.

12. A process for producing a *Streptococcus suis* capsular antigen, said method comprising:

using the protein or fragment of claim 11 to prepare said *Streptococcus suis* capsular antigen.

13. A *Streptococcus suis* capsular antigen produced by the process of claim 12.

14. A vaccine comprising:

the *Streptococcus suis* capsular antigen of claim 13 in an amount sufficient to produce an immune response in a subject, and

a suitable carrier or adjuvant.

15. A recombinant *Streptococcus suis* mutant having a modified capsular gene cluster.

16. A recombinant microorganism comprising at least a part of a capsular gene cluster of *Streptococcus suis*, wherein said capsular gene cluster comprises a deletion, insertion or (point)-mutation.

17. The recombinant microorganism of claim 16, wherein said recombinant microorganism comprises a lactic acid bacterium.

18. A vaccine comprising the recombinant *Streptococcus suis* mutant of claim 15 or the microorganism of claim 16 or claim 17.

19. The vaccine of claim 18, wherein said vaccine [comprises a Streptococcus mutant] includes a Streptococcus mutant deficient in capsular expression.

20. The vaccine of claim 19, wherein said Streptococcus mutant deficient in capsular expression is a recombinant Streptococcus mutant.

21. The vaccine of claim 19 or claim 20, wherein said Streptococcus mutant deficient in capsular expression is capable of surviving in an immune-competent host.

22. The vaccine of claim 21, wherein said Streptococcus mutant deficient in capsular expression is capable of surviving at least 4-5 days in said immune-competent host.

23. The vaccine of any one of claims 19 to 22, wherein said Streptococcus mutant deficient in capsular expression expresses a *Streptococcus* virulence factor or antigenic determinant.

24. The vaccine of any of claims 19 to 23, wherein said Streptococcus mutant deficient in capsular expression expresses a *non-Streptococcus* protein.

25. The vaccine of claim 24 wherein said non- *Streptococcus* protein has been derived from a pathogen.

26. A method for controlling or eradicating a Streptococcal disease in a population, said method comprising:

vaccinating subjects in said population with the vaccine of any one of claims 18 to 25.

27. A method for controlling or eradicating a Streptococcal disease, said method comprising:

testing for the presence of encapsulated Streptococcal strains in a sample collected from at least one subject in a population partly or wholly vaccinated with a vaccine of any one of claims 18 to 25.

28. A method for controlling or eradicating a Streptococcal disease comprising testing for the presence of capsule-specific antibodies directed against Streptococcal strains in a sample collected from at least one subject in a population partly or wholly vaccinated with a vaccine of any one of claims 18 to 25.

29. A method for controlling or eradicating a Streptococcal disease in a population comprising:

selecting subjects in said population vaccinated with a vaccine according to any one of claims 18 to 25; and

testing a sample collected from at least one subject in said population for the presence of encapsulated Streptococcal strains and/or for the presence of capsule-specific antibodies directed against Streptococcal strains.

ABSTRACT OF THE DISCLOSURE

The invention relates to *Streptococcus suis* infection in pigs, vaccines directed against those infections and tests for diagnosing *Streptococcus suis* infections. The invention provides an isolated or recombinant nucleic acid encoding a capsular gene cluster of *Streptococcus suis* or a gene or gene fragment derived thereof. The invention further provides a nucleic acid probe or primer allowing species or serotype-specific detection of *Streptococcus suis.* The invention also provides a *Streptococcus suis* antigen and vaccine derived thereof.

N:\2183\4726\Redlined app - Appendix B.wpd

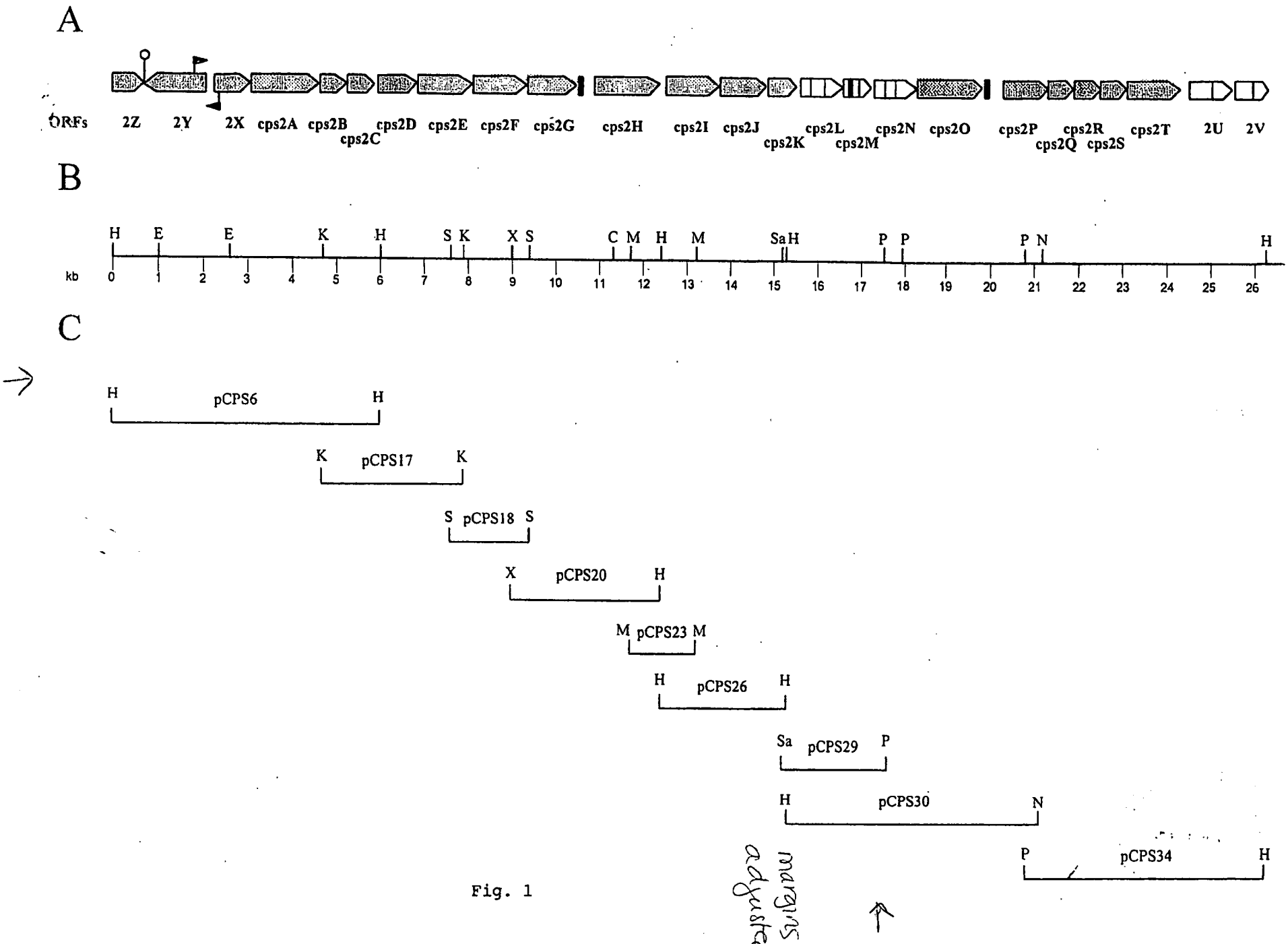

Fig. 1

marginis adjusted

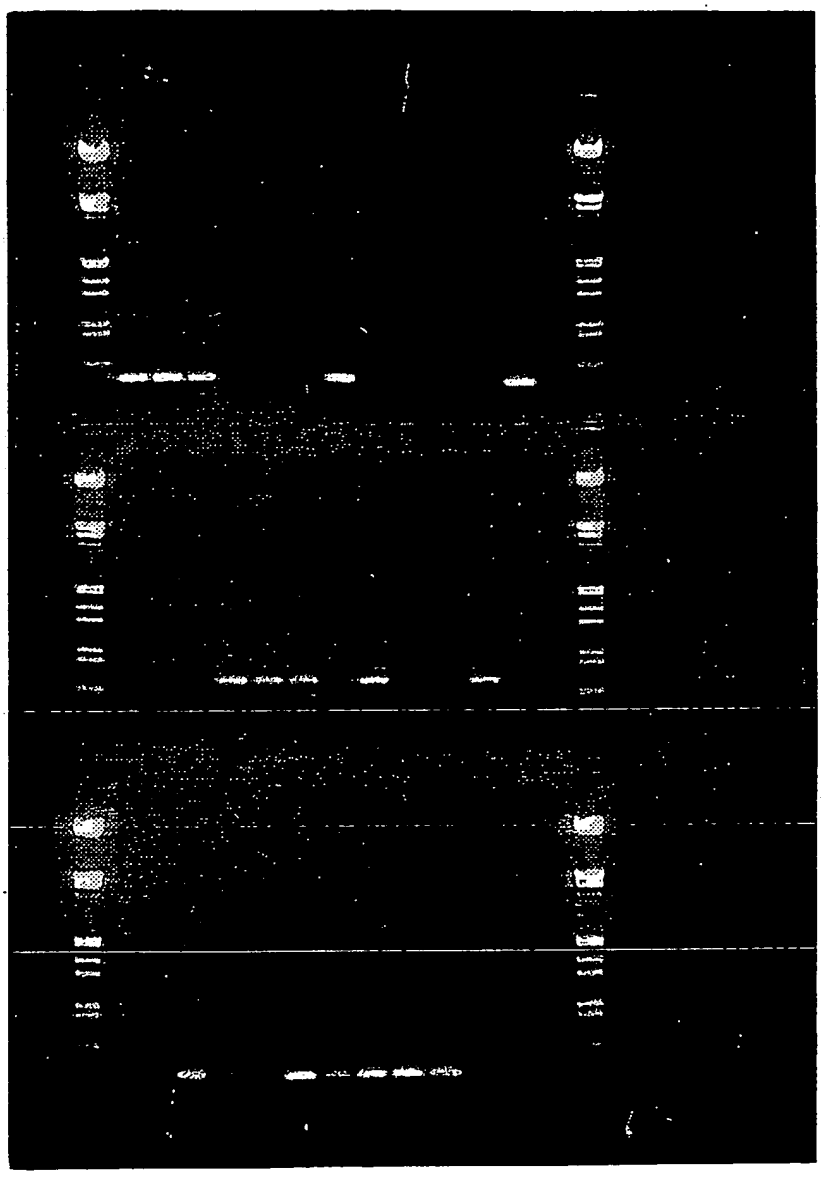

Fig. 2

better copy provided

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GGTCGAATTG TTATGGCCCA CCGCAACAAT GCTAAGTTCT TCCAACAATT CTCAGAGTTG
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GCCAAGGTTT CCATTTGTGT GAGAATATAT AGAGCTTGTT GACTACCAGC
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CGCATATTTA CAGCGCTCTT ACTTGTTTTT TCACTGGTCA TCACGTCTGT

margin requirements supplied with

Fig. 3 DNA Serotype 2

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Fig. 3 cont.

revised to comply with margin requirements

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revised to satisfy margin requirements

Fig. 3 cont.

change margins

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ACAAATCAGA TGGCGCTCAT TGAATCTGGC GTGGATATGT GGGAAACGGC
GAGAGAAGCC TCTTATTCAG GTTATGATTG TAATGTTATA CATGCACCAA TTGATTTAAG
TTTTTGTAAA GAAAATATTG TAATAAAATA TAACGAACTA TCCAGAGAAA
CAGTAGCAGA ACGCGTGATG AAAACGGGAA GAGAAATGGC TGTTCGTGCA TATAATGTGG
AGCGAAAACA AAAAGAAAAG AAATTTCTAA AACCTATTAT ATTTGTATTA
GATGGGTTAA AAGGAGATGA GTATATTCAT CCCAATCCAT CAAATCATTT GACGATCTTA
ACTGAAATGT ATAACGTCAG AGGCTTACTT ACCGATAATC ACCAAATTAA
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TGCAGCGGAT TTGGCATATG GGGATTTAAC TTTAGACTAT GCTATAAGGG TTAGACGCGT
TTTAGGTTGG AATGGAACGC TTGAAATGCC CTTACTGAGT ATTATGTTAA

Fig. 3. cont.

revise margins

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ATCATTGTAG TCCTATCTGC AACAGTAGAA AATTATATTG TAAATTTAAG TTTTGTATTT
ATGCCAATAT GTTTTTGTTT ATTAAATTCT ATATCTACTA TGGAATCAAC
TATTAACAAA CAACTGCAAA CATAAATTGG CAGGAATAGA GTTTTGAGTT GCTATTAATT
TGGTAGAGCA TATGTTCTAT AGGTGGCAAG ATAAAGATAG TATTTTTTAC
ATGATGATTT TTATGATAGC AAAGCAAGTT ACGGCATAAA AGGAATTAGA GGATGGAAAA
AGTCAGCATT ATTGTACCTA TTTTTAATAC GGAAAAGTAC TTAAGAGAGT
GTTTAGATAG CATTATTTCC CAATCGTATA CTAATCTAGA GATTCTTTTG ATAGATGACG
GTTCTTCAGA TTCATCAACG GATATATGTT TGGAATACGC AGAGCAAGAT
GGTAGAATAA AACTTTTCCG GTTACCAAAT GGTGGTGTTT CAAACGCAAG GAATTACGGT
ATCAAAAATA GCACAGCAAA TTATATTATG TTTGTAGATT CTGATGATAT
TGTTGACGGC AACATTGTTG AGTCCTTATA CACCTGTTTA AAAGAGAATG ATAGTGATTT
GTCGGGAGGG TTACTTGCTA CTTTTGATGG AAATTATCAA GAATCTGAGC
TGCAAAAGTG TCAAATTGAT TTGGAAGAGA TAAAAGAGGT GCGAGACTTA GGAAATGAAA
ATTTTCCCAA TCATTATATG AGCGGTATCT TTAATAGCCC TTGTTGCAAA
CTTTATAAGA ATATATATAT AAACCAAGGT TTTGACACTG AACAGTGGTT AGGAGAGGAC
TTATTATTTA ATCTAAATTA TTTAAAGAAT ATAAAAAAAG TCCGCTATGT
TAACAGAAAT CTTTATTTTG CCAGAAGAAG TTTACAAAGT ACTACAAATA CGTTTAAATA
TGATGTTTTT ATTCAATTAG AAAATTTAGA AGAAAAAACT TTTGATTTGT
TTGTTAAAAT ATTTGGTGGA CAATATGAAT TTTCTGTTTT TAAAGAGACG CTACAGTGGC
ATATTATTTA TTATAGCTTA TTAATGTTCA AAAATGGAGA TGAATCGCTT
CCAAAGAAAT TGCATATATT TAAGTATTTA TACAATAGGC ATTCTTTAGA TACTCTAAGT
ATTAAACGAA CGTCCTCTGT TTTTAAAAGA ATATGTAAAT TAATTGTTGC
TAATAATTTG TTTAAAATTT TTTTAAATAC TTTAATTAGG GAAGAAAAAA ATAATGATTA
ACATTTCTAT CATCGTCCCA ATTTACAATG TTGAACAATA TCTATCCAAG
TGTATAAATA GCATTGTAAA TCAGACCTAC AAACATATAG AGATTCTTCT GGTGAATGAC
GGTAGTACGG ATAATTCGGA AGAAATTTGT TTAGCATATG CGAAGAAAGA
TAGTCGCATT CGTTATTTTA AAAAAGAGAA CGGCGGGCTA TCAGATGCCC GTAATTATGG
CATAAGTCGC GCCAAGGGTG ACTACTTAGC TTTTATAGAC TCAGATGATT
TTATTCATTC GGAGTTCATC CAACGTTTAC ACGAAGCAAT TGAGAGAGAG AATGCCCTTG
TGGCAGTTGC TGGTTATGAT AGGGTAGATG CTTCGGGGCA TTTCTTAACA
GCAGAGCCGC TTCCTACAAA TCAGGCTGTT CTGAGCGGCA GGAATGTTTG TAAAAAGCTG
CTAGAGGCGG ATGGTCATCG CTTTGTGGTG GCCTGGAATA AACTCTATAA
AAAAGAACTA TTTGAAGATT TTCGATTTGA AAAGGGTAAG ATTCATGAAG ATGAATACTT
CACTTATCGC TTGCTCTATG AGTTAGAAAA AGTTGCAATA GTTAAGGAGT
GCTTGTACTA TTATGTTGAC CGAGAAAATA GTATCATAAC TTCTAGTATG ACTGACCATC
GCTTCCATTG CCTACTGGAA TTTCAAAATG AACGAATGGA CTTCTATGAA
AGTAGAGGAG ATAAAGAGCT CTTACTAGAG TGTTATCGTT CATTTTTAGC CTTTGCTGTT
TTGTTTTTAG GCAAATATAA TCATTGGTTG AGCAAACAGC AAAAGAAGCT
TCTCCAAACG CTATTTAGAA TTGTATATAA ACAATTGAAG CAAAATAAGC GACTTGCTTT
ACTAATGAAT GCTTATTATT TGGTAGGGTG TCTTCATCTT AATTTTAGTG
TCTTTCTGAA AACGGGGAAA GATAAAATTC AAGAAAGATT GAGAAGAAGT GAAAGTAGTA
CTCGGTAAGA ATGTTGTAAT AAATGGTTGA AAGAAAAGGG GATTAAAATG
AATCCAACAA ATAGTAGAAT AGCACTCTTT GATACGATTA AATGTATCAT GGTACTTTGT
GTTATTTTTA CACATCTGGA TTGGTCTGTT GAGCAGCGTC AATGGTTTAT
CTTTCCGTAT TTCGTTGACA TGGCTGTTCC AATTTTTCTG TTGCTTTCTG CCTATTTTCG
AACGAATAAG TGGAATACAA AACAAGAGAC GCTAAAGCTC AAGTTCAGCA
GTGGTATAAA AGAAAGTATA AACATGCTTT GTCTCTATGC TATCGTGATG GCTGTTAATG
TTTTATTGAG CTATTCGAGA ACCATCTGAT AGGAGTAAAG CCTTTTTCAG
GTTCTTCATC GCTCCGTTCA TTTGTCCTGT GGCTACTTTC TGGAGAATCG GGTCCAGGGA
GTTGGGAGTT ACTATGTTCC GTTGTTGATT CAGGTAGTTT TTTTATTACC
AATTTTGTAT GTTCTTTTCG AGAAAAATAA ATGGTTGGGC TTGCTTACTT GTTTTTTAGT
AAACTTTTCA GTGGATGCCA TATTTGCTAA CATGGCTGAA CACGGCATAT
ATATATAGAC TAATATCACT TCGTTATCTT TTTGTTCTAG GGCTTGGTTT TTTCTTTCAA
AGCAGGATGT GCGTTCCAAG GTAGATACTT TCATTGCGAC CCTATTTGGG
ATTATTGGAG CAATTCTGAT TTTTGTGAAT CATTCTATAG AGCCCTTCTC CTGGTTTTAT
GGTTGGAAGT CTACTTCCTT TCTATGCGTC CCATTTGCGT ATGCTATGCT
ATTTTTTATG ATAAAGTATG GACAGAAGAT TCCAGCAATA CTGTTGTCAA AATTGGGAGT
TGCTTCTTAT CATATCTACT TGACCCAGAT GCTGTATTTT TCAGTAGTCG

Fig. 3 cont.

change margins

CACCATTTTT AGCAGTGCAA TTTAAGGTAT CTTCGTTGAA TTTGTGGAAC GGCTTGTTTA
CCTTTCTAAT TTGCCTGTTT GGTGGCTATA TTTTCTACAA AGTGGATCTG
TTTATGAGAG TACGTGGAAA ACGATAATGA CTCATTTCAG ATTAGCAGAT GCCATTTCGT
TTATTAGCAG ATTCGCATGT TAATATTCCG ACAAAGAAAT TCAAATAGGT
TGACGAGAGA GGAGTGGTAT CTGTTTCTAA ACCCCAGTAT CCCCCTTTAT TTTCAAAGCT
ATATTTATTA ACTGAACAAG GAGAATTTTT AAGAGAACTG TTTGTTTAAT
CCCAGCACGA TCTGGTTCGA AAGGCTTACC GAATAAAAAC ATGCTATTTT TGGACGGGAA
ACCCATGATT TTTCACACGA TTGATGTGGC AATTGAATCA GGTTGTTTTG
AGAAAGAAGA CATCTATGTC AGTACGGATT CAGAAATGTA TAAGGGGGGC ACCTCTATAA
ATTCCCAAAA TTGCGAATTT GGAGTTACGA AAGCCTTGTT AAATCAACAT
CTTAAATTTT AGAAAATTAG TTTTTAGAGG TCCCCAAGGG GATTTGCGAG ACAAGAGGCA
TCAATGTATT GTTAAGACCC AAAGAACTAT CTACTTATCA TACTCCATCG
AATGAAGTCA GTACGCACTT TTTTACGAAT CTGGATTTTA TGAAGATTGT ATATTTGTTC
TTCTGCAAGT CACCTCACCG TTACGGACTG GCGAACAGAT AAAAGAAGCC
ATGAATATGT ACTTACAGGG GGACTCAGAA AATGTTTTGC ATTTCAATGA TGAAGGGCAA
GAAAGAGTGA ATCAGTACAT TATCGAAGCT GTACAGGGGT TATAAAAAGG
GGTTACTTAT CCTTAAAGTC TGTATGTAGA AGGAGAAAAA TTGAGACGAA TTTATATTTG
CCATACGATG TATCAGATCC TGATTTCCTT GTTAAAGATG GACGTTGAGA
GAGATAGTTT GATGTCCGTT GATATCATCG GGCATTTTCC AGATGTCAGG GAGCAACTGC
AGCAGCATGT TCATCTAATC GAGGGAGACG GAGCGTTCAT TTGATCTATA
TTCTTTGATA GCTAGATCAA AAACAAAAGA ACGCCTTTCC TTGTTACAGA GCTATGACGA
GGTGATCATT TTTCAAGATC ACCGTCAAGT CGGTCATTTT TTAAATAAAC
ATCGGATTCC CTATTCTCTT TTGGAGGATG GTTATAATTT TTTCAAGGAT AAAAGAGTGT
GCGATTTGGA GTCAATTCAA TCATCTGTCT GGAAAAGACT CTTTTATCAA
TGGTATTTTA AACCAACATA TTTGATTGGT TCAAGTCTCT ATTGTCAATC CATTGAGGTC
AATGATCTGT CGCTCGTACA ATTTGACTAG GCTTATAAAC CCTTTGTAGA
AGTTCCGAGA AAGCAATTAT TTGATCAAGC ATCGCCAGAG AAGGTGCAAG CGCTGCTGCA
GATATTTGGA GCAAGGGCGA TAGTAGCGGA TGAAGAGTCT TCTCAAAAAC
GATTGCTATT ATTGACCCAG CCCTTGTCTT GGGATTATCA TGTGACCGAA GAGAGTTGTT
GGAGATTTAT GTAGCAGGTC TTGCCCCTTA TCGGGAAGAC TATACAATCT
ACATAAAACC GCACCCACGA GATGGGGTTG ATTATTCATT TCTGGGTAAG GCTGTGGTGC
TTCTGCCTCA AGGTATTCCG TTTGAGTTGT TCGAAATGGC AGGTAATATC
CGTTTTGATA TCGGTATGAC CTATAGTTCG TCTGCTTTAG ATTTTTTAAA TTGTTTTGAA
GAGAAAGTGT ATTTAAAGGA CACTTTTCCT CTTCTTTCAA AAAATGATAT
TTTGCGTGAG GGGATAGAAT AGGAGGATTC ATGTCTAAAA AATCAATAGT TGTCTCAGGT
CTCGTCTATA CGATTGGAAC CATCCTCGTT CAGGGATTAG CCTTCATTAC
CCTCCCCATC TATACTCGTG TCATTTCTCA GGAAGTATAT GGGCAGTTTA GCTTGTATAA
TTCGTGGGTG GGGCTAGTTG GTCTCTTTAT CGGTCTACAG TTAGGTGGGG
CTTTTGGCCC GGGATGGGTA CACTTCCGCG AGAAATTTGA TGATTTCGTA TCCACCTTGA
TGGTCTCTTC TATCGCTTTC TTTTTACCAA TTTTTGGGCT ATCTTTTCTC
CTCAGTCAGC CCCTATCGCT CCTATTTGGT TTGCCTGATT GGGTCGTTCC GCTTTACTTT
TTGCAAAGTT TTATGAGTGT TGTGCAAGGA TTTTTTACGA CCTATTTAGT
GCAGCGGCAG CAGTCCATGT GGACTTTACT CCTATCGGTA CTGAGCGCTG TTATCAACAC
TGCTTTATCT TTATTTCTCA TCTTTTCGAT GGAGAATGAT TTCATCGCTC
GTGTAATGGC AAACTCGGCA ACGACTGGTG TTTTTGCTTG TGTGTCCTTG TTGTTTTTCT
ATAAGAAGAT TGGGCTTCAT TTTCGAAAGG ACTATCTTCG GTATGGTTTA
AGTATATCGA TTCCTCTTAT TTTTCATGGA TTAGGTCATA ATGTACTCAA TCAATTTGAC
AGAATCATGC TCGGCAAGAT GCTAACACTG TCAGATGTAG CCCTATACAG
TTTCGGCTAC ACACTTGCGT CTATCTTACA AATTGTGTTT TCGAGCTTGA ATACGGTATG
GTGTCCGTGG TATTTTGAGA AAAAGAGAGG TGCAGATAAA GATTTGCTCA
GTTATGTCCG TTACTATCTG GCGATTGGCC TGTTTGTGAC TTTTGGATTT CTAACAATTT
ACCCTGAATT AGCGATGTTG TTAGGTGGAT CTGAGTATCG TTTCAGTATG
GGATTTATTC CCATGATTAT TGTCGGGGTG TTCTTTGTAT TTCTTTATAG TTTTCCAGCC
AATATCCAGT TTTATAGTGG AAATACAAAG TTTTTGCCAA TTGGTACTTT
TATAGCAGGT GTACTAAATA TTTCCGTCCA CTTTGTTTTG ATACCGACAA AGAATTTATG
GTGCTGCTTT GCAACGACTG CTTCCTATCT GTTGTTGCTA GTCTTGCATT
ATTTTGTTGC TAAGAAAAAG TATGCTTACG ATGAAGTTGC GATTTCAACA TTTGTTAAGG
TAATTGCTCT TGTTGTCGTC TATACAGGCT TGATGACAGT ATTTGTCGGT
TCAATCTGGA TTCGTTGGTC ACTAGGAATA GCGGTTCTAG TCGTTTATGC CTACATTTTT
AGAAAGGAAT TAACAGTTGC CCTCAATACA TTCAGGGAAA AACGGTCTAA

Fig. 3 cont.

change margins

ATAAGGGCAC CTCTATAAAC TCCCAAAATT GCGAATTTGG AGTTACGAAA GCCTTGTTAA
ATCAAACATT TTAAATTTTA GAAAATTAGT TTTTAGAGGT CCCCATATAA
AAACGTCCCA AATGAGAGGT GCTCATAAGA ATTGACCATC ACTGCCATCT ACCCAAAGTT
CAAGTATTCT CTACCATGAA AATTGTGCTA TAATCAAGTA TAAAGAAGGG
AATGTTTCTT AAAGGACGTA TGCGCCTCTG CTTATGCCAG AAGTCATGAG GTAAATCTCC
CTAAAAATTG GGTAGAAAAG CAGATTAAAC TTCCACCAAT CTATTGAAGA
TCGTGTTGAA GAGCAGGCTT TAGAAGCAAC AAGCCCTGAG ACTATTCGAA AGAAATCTAG
GGCTATTTTT TCTAATCGGC TATCAGAAGT GAAGTAGCGA TCTTTATTAG
TGTTCTTTTA CTACTTAAGG AAAACCAAGC TGCTCCCTCA AGACTTTATG GGAGCGATTT
ACAGTCATTT TTAGAAAGGA AATAAAATGG TTTATATTAT TGCAGAAATT
GGTTGTAATC ACAACGGTGA TGTTCATCTA GCACGGAAAA TGGTAGAAGT TGCCGTTGAT
TGTGGTGTGG ATGCCGTTAA ATTTCAGACA TTTAAGGCAG ATTTGTTGAT
TTCAAAATAC GCACCAAAGG CCGAATACCA AAAAATTACA ACAGGAGAGT CAGATTCTCA
GCTCGAAATG ACTCGTCGTT TGGAATTGAG CTTTGAAGAG TATCTTGATT
TGCGTGATTA CTGTCTTGAA AAGGGAGTTG ATGTGTTTTC GACACCTTTT GATGAGGAAT
CATTGGACTT CTTGATTAGC ACAGATATGC CCGTTTATAA GATTCCATCT
GGTGAGATTA CCAATCTTCC CTATTTGGAA AAAATTGGTC GTCAAGCTAA GAAAGTTATT
CTTTCAACTG GTATGGCTGT TATGGATGAA ATTCATCAAG CGGTGAAGAT
TTTGCAGGAA AATGGAACGA CCGATATTTC GATTTTGCAT TGTACAACCG AGTATCCAAC
CCCTTACCCT GCTTTGAATT TGAATGTCTT GCATACCTTG AAAAAAGAAT
TTCCAAACTT AACAATTGGC TATTCAGACC ATAGTGTTGG TTCAGAAGTA CCCATCGCTG
CTGCAGCAAT GGGAGCTGAA TTGATTGAAA AGCACTTTAC TCTGGACAAT
GAAATGGAAG GACCAGATCA TAAAGCGAGT GCTACTCCTG ATATCTTAGC AGCCTTGGTA
AAAGGAGTGA GGATAGTGGA ACAATCTCTT GGTAAATTTG AAAAAGAGCC
AGAAGAAGTT GAAGTACGAA ATAAAATTGT AGCTAGAAAA TCTATTGTTG CCAAAAAAGC
AATTGCTAAA GGCGAAGTCT TTACAGAAGA AAACATCACT GTCAAAAGAC
CAGGAAATGG AATTTCGCCA ATGGAATGGT ACAAAGTCTT GGGGCAGGTG AGTGAGCAGG
ATTTTGAGGA AGACCAAAAT ATTTGCCATA GTGCTTTTGA AAATCAAATG
TAAGCGGAGT AAGGATGAAA AAAATTTGTT TTGTGACAGG CTCTCGTGCC GAATATGGGA
TTATGCGTCG CTTATTGAGC TATCTACAGG ATGATCCAGA AATGGAGCTG
GATCTTGTAG TGACAGCCAT GCATCTAGAA GAAAAATATG GGATGACGGT CAAAGACATC
GAAGCGGACA AGCGTAGGAT TGTCAAGCGG ATTCCATTGC ATTTGACGGA
TACGTCTAAG CAGACAATCG TCAAATCTTT AGCGACCTTG ACAGAGCAAC TCACGGTTCT
TTTTGAAGAA GTCCAGTATG ACTTGGTGTT GATTCTGGGG GATCGCTATG
AGATGCTACC AGTTGCCAAT GCTGCGTTGC TTTATAATAT TCCTATTTGC CATATTCATG
GTGGTGAAAA AACCATGGGA AATTTTGATG AGTCGATTCG CCATGCCATT
ACCAAGATGA GTCACCTTCA TCTGACATCA ACGGATGAAT TTAGAAATCG TGTCATTCAA
CTAGGAGAAA ATCCAACCAT GTACTGAACA TCGGAGCTAT GGGTGTTGAA
AATGTTTTAA AACAAGACTT TTTGACAAGA GAAGAGTTGG CGATGGAACT TGGAATTGAT
TTTGCCGAGG ATTACTATGT TGTACTCTTT CACCCTGTTA CCTTGGAGGA
TAACACAGCC GAAGAACAAA CGCAGGCCTT ATTAGATGCT CTAAAAGAAG ATGGTAGCCA
GTGTTTGATA ATTGGATCCA ATTCGGATAC ACATGCCGAT AAGATAATGG
AATTGATGCA TGAATTTGTA AAACAAGACT CTGATTCTTA CATCTTTACT TCGCTTCCAA
CTCGTTATTA CCATTCCTTG GTCAAGCATT CACAAGGTTT AATAGGGAAT
TCTTCGTCAG GTTTGATTGA AGTGCCCTCA TTACAGGTTC CGACCTTAAA TATTGGAAAT
CGCCAATTTG GACGTTTGTC AGGACCGAGT GTGGTACATG TTGGAACTTC
TAAGGAAGCG ATTGTTGGTG GTTTGGGGCA ATTACGTGAT GTGATAGATT TTACCAATCC
ATTTGAACAA CCTGATTCTG CTTTACAAGG TTATCGAGCT ATCAAGGAAT
TTTTATCTGT ACAGGCCTCA ACCATGAAAG AGTTTTATGA TAGATAGGGG AGAAAGTTTG
ATGAAAAAAG TAGCCTTTCT AGGAGCGGGT ACCTTTTCAG ATGGTGTCCT
TCCTTGGTTG GATAGAACTC GATATGAACT CATTGGATAT TTTGAAGATA AACCGATCAG
TGACTATCGT GGCTATCCTG TATTTGGTCC CTTGCAAGAT GTCCTAACCT
ATTTGGATGA TGGAAAAGTA GATGCTGTCT TCGTCACTAT AGGTGACAAT GTCAAGCGCA
AGGAAATCTT TGACTTGCTT GCCAAAGATC ATTATGATGC TTTGTTCAAC
ATCATTAGCG AGCAAGCCAA TATTTTTTCC CCAGATAGTA TCAAGGGACG AGGGGTTTTC
ATAGGTTTTT CAAGTTTTGT AGGAGCCGAT TCCTATGTCT ATGACAATTG
TATCATCAAT ACGGGTGCCA TTGTGGAACA TCATACCACG GTGGAGGCCC ATTGTAACAT
TACTCCAGGA GTGACCATAA ATGGCTTGTG CCGTATCGGA GAAAGCACTT
ATATTGGAAG TGGTTCAACA GTGATTCAAT GTATCGAGAT TGCACCTTAT ACAACATTGG
GGGCAGGGAC AGTTGTTTTG AAATCGTTGA CGGAGTCAGG GACCTATGTT

Fig. 3 cont.

revise margins

GGTGTACCTG CTAGAAAGAT TAAATAGGTG AATTGATGGA ACCAATTTGT CTGATTCCTG
CTCGGTCAGG ATCAAAAGGT TTACCAAATA AAAACATGTT ATTTTTAGAT
GGTGTACCGA TGATTTTCCA TACCATTCGA GCTGCGATTG AGTCTGGATG TTTTAAGAAA
GAAAATATAT ATGTCAGTAC TGATTCAGAG GTTTACAAGG AAATTTGTGA
AACAACTGGG GTTCAAGTCC TCATGCGTCC AGCTGACTTG GCGACAGATT TTACAACCTC
TTTTCAACTG AACGAACATT TTTTACAAGA TTTTTCTGAT GACCAAGTAT
TTGTTCTCCT GCAAGTTACG TCCCCATTAA GATCGGGAAA ACATGTCAAG GAGGCGATGG
AGTTATATGG GAAAGGTCAA GCTGACCACG TTGTTAGCTT TACCAAAGTC
GATAAGTCTC CAACATTGTT TTCAACTTTA GACGAAAACG GATTCGCTAA GGATATTGCA
GGATTAGGTG GCAGTTATCG TCGTCAAGAT GAGAAAACAC TCTACTATCC
TAATGGAGCG ATTTATATTT CTTCTAAGCA GGCTTATTTA GCGGATAAAA CTTATTTTTC
TGAAAAAACA GCGGCCTATG TGATGACGAA GGAAGATTCG ATTGATGTAG
ATGATCACTT TGATTTTACT GGTGTTATTG GTCGAATTTA CTTTGATTAC CAGCGTCGTG
AGCAACAAAA CAAACCATTT TATAAAAGAG AGTTAAAGCG TTTATGTGAG
CAACGAGTCC ATGATAGTCT TGTGATTGGC GATAGTCGTC TGTTAGCCTT GTTACTGGAT
GGTTTCGATA ATATCAGCAT CGGTGGGATG ACAGCTTCGA CAGCACTTGA
AAACCAAGGT CTCTTTTTGG CTACTCCGAT AAAGAAAGTT TTGCTTTCTC TTGGTGTGAA
TGATTTGATT ACTGACTATC CCTTGCATAT GATTGAGGAT ACTATTCGCC
AGCTGATGGA AAGTCTTGTT TCCAAAGCAG AGCAGGTTTT TGTGACGACG ATTGCCTACA
CGCTGTTTCG TGATAGCGTT TCCAATGAAG AAATTGTGCA GCTGAATGAC
GTTATTGTTC AGTCAGCAAG TGAACTGGGT ATTTCAGTGA TTGATCTAAA TGAAGTTGTT
GAAAAAGAGG CGATGCTTGA CTATCAGTAT ACCAATGATG GATTGCATTT
CAATCAGATT GGACAAGAGC GTGTGAATCA GCTGATTTTG ACAAGTTTGA CAAGATAATT
TGGTGATAGA AGCTATTTCA GTGGCTAGAC TATGTTGGTA TGTGTTTTAG
AGCCCAGGAA TAACATCTGT AGAGGATGCT AGCCTTGAGA ATTGACAACC ATTTAGTTGT
TTTAATTATA TAAGGGGACC TCTAAAAACT CCCTAAATTT CCCAAAAATG
AGATAATAGA ATAAAAAGTA ATGAGGAGAG CTGTCATGCA TTTATTCACA GACGATGAAA
AAATCTTGTC AAAACTATCA GAGAAAGGCA ATCCCTTAGA ACGTTTGGAT
GCCGTTATGG ATTGGAATAT CTTTCTTCCA TTGTTGTCAG AGTTATTCAG TCGTAAAGAT
AAAGTCATCA GTCGTGGCGG TCGTCCTCAC CTAGACTATC TCATGATGTT
CAAAGCGCTC TTGCTTCAAC GTCTTCATAA CCTATCTGAC GATGCCATGG AATATCAACT
GCTGGATCGT ATATCTTTTC GTCGTTTTGT TGGTTGTCAT GAAGACACTG
TTCCCGATGC GAAAACTATC TGGCTCTATC GTGAGAAATT AACCAAGTCA GGTCGTGAAA
AGGAGTTGTT CGATTTGTTC TATGCCCATC TCACAGATGA AGGGGTGATT
GCCCATTCAG GTCAGATTGT GGATGCTACC TTTGTCGAAT GCCCTAAACA ACGCAATTCA
CGTGAGGACA ATCAGAAAAT CAAAACTTAT CGAAAATTAT GAGGTCACAA
CAGCTAGTGT ACACGACTCC AATGTCCTAG CTCCTCTTTG TGATGCCAAT GAAGCGGTTT
TTGATGACAG TGCTTATGTT GGAAAATCAG TACCAGAAGG TTGTCGCCAC
CACACGATTC GTCGTGCTTT TAGAAATAAA CCGTTGACTG AGACTGATAA GGTCATTAAT
CGACATATTA CCAAAGTCCG TTGTCGCGTT GAGCATGGTT TTGGCTTCAT
TGAAACTAAC ATGAAAGGTA ACATCTGTCG AGCAATTGGG AAGGCACGAG CTGAAACCAA
TGTGACCTTA ACCAACCTGC TCTACAATAT CTGTCGTTTT GAGCAAATCA
AACGACTGGG ATTACCATCC GTGGGCTTAG TGCGCCCAAA AAATAGGAAA ATAAGCAAAA
AGAGGCTGGG CAAAAACTAG TTTCTCACAA TAAAAAAACG GCTCTTTGTC
AACTGTAGTG GGTAGACGAA AAGCTAACAC CTAGAGAGGA CGAAATTCGT TCTCTCATTT
TTGATGTTTA AAGCGTAACC GCCTAATAAC AAGGTATCTA TCCAATCACA
CATTCCTCCA TTATATAGTT AAATGAAACA AAAACAGTAC ATCTATGATA TAATGTATTT
ATGGCATATT CATTAGATTT TCGTAAAAAA GTTCTCGCAT ACTGTGAGAA
AACCGGCAGT ATTACTGAAG CATCAGCTAT TTTCCAAGTT TCACGTAACA CTATCTATCA
ATGGCTAAAA TTAAAAGAGA AAACCGGCGA GCTTCATCAC CAAGTTAAAG
GAACCAAGCC AAGAAAAGTG GATAGAGATA AATTAAAGAA TTATCTTGAA ACTCATCCAG
ATGCTTATTT GACTGAAATA GCTTCTGAAT TTGACTGTCA TCCAACAGCT
ATTCATTACC CCCTCAAAGC TATGGGATAT ACTCGAAAAA AAAGAGCTGT ACCTACTATG
AACAAGACCC TGAAAAAGTA GAACTGTTCC TTAAAGAATT GAATAACTTA
AGCCACTTGA CTCCTGTTTA TATTGACGAG ACAGGGTTTG AGACATATTT TCATCGAAAA
TATGGTCGCT CTTTGAAAGG TCAGTTGATA AAAGGTAAGG TCTCTGGAAG
AAGATACCAG CGGATATCTT TAGTAGCAGG TCTCATAAAT GGTGCGCTTA TAGCCCCGAT
GACATACAAA GATACTATGA CGAGTGGCTT TTTCGAAGCT T

Fig. 3 cont.

SEQ. ID. NO. 9

SLDIDHMMEVMEASKSAAGSACPSPQAYQAAFEGAENIIVVTITGGLSGSFNAARVARDM
YIEEHPNVNIHLIDSLSASGEMDLLVHQINRLISAGLDFPQVVEAITHYREHSKLLFVLA
KVDNLVKNGRLSKLVGTVVGLLNIRMVGEASAEGKLELLQKARGHKKSVTAAFEEMKKAG
YDGGRIVMAHRNNAKFFQQFSELVKASFPTAVIDEVATSGLCSFYAEEGGLLMGYEVKA

Fig. 3 cont. ORF2Z

SEQ. ID. NO. 10

change margins

MKKYQVIIQDILTGIEEHRFKRGEKLPSIRQLREQYHCSKDTVQKAMLELKYQNKIYAVE
KSGYYILEDRDFQDHTCRAQSYRLSRITYEDFRICLKESLIGRENYLFNYYHQQEGLAEL
ISSVQSLLMDYHVYTKKDQLVITAGSQQALYILTQMETLAGKTEILIENPTYSRMIELIR
HQGIPYQTIERNLDGIDLEELESIFQTGKIKFFYTIPRLHNPLGSTYDIATKTAIVKLAK
QYDVYIIEDDYLADFDSSHSLPLHYLDTDNRVIYIKSFTPTLFPALRIGAISLPNQLRDI
FIKHKSLIDYDTNLIMQKALSLYIDNGMFARNTQHLHHIYHAQWNKIKDCLEKYALNIPY
RIPKGSVTFQLSKGILSPSIQHMFGKCYYFSGQKADFLQIFFEQDFADKLEQFVRYLNE

Fig. 3 cont. ORF2Y

SEQ. ID. NO. 53

revise margins

MKIIIPNAKEVNTNLENASFYLLSDRSKPVLDAISQFDVKKMAAFYKLNEAKAELEADRW
YRIRTGQAKTYPAWQLYDGLMYRYMDRRGIDSKEENYLRDHVRVATALYGLIHPFEFISP
HRLDFQGSLKIGNQSLKQYWRPYYDQEVGDDELILSLASSEFEQVFSPQIQKRLVKILFM
EEKAGQLKVHSTISKKGRGRLLSWLAKNNIQELSDIQDFKVDGFEYCTSESTANQLTFXR
SIKM

Fig. 3 cont. ORF2X

SEQ. ID. NO. 11

change margins

MKKRSGRSKSSKFKLVNFALLGLYSITLCLFLVTMYRYNILDFRYLNYIVTLLLVGVAVL
AGLLMWRKKARIFTALLLVFSLVITSVGIYGMQEVVKFSTRLNSNSTFSEYEMSILVPAN
SDITDVRQLTSILAPAEYDQDNITALLDDISKMESTQLATSPGTSYLTAYQSMLNGESQA
MVFNGVFTNILENEDPGFSSKVKKIYSFKVTQTVETATKQVSGDSFNIYISGIDAYGPIS
TVSRSDVNIIMTVNRATHKILLTTTPRDSYVAFADGGQNQYDKLTHAGIYGVNASVHTLE
NFYGIDISNYVRLNFISFLQLIDLVGGIDVYNDQEFTSLHGNYHFPVGQVHLNSDQALGF
VRERYSLTGGDNDRGKNQEKVIAALIKKMSTPENLKNYQAILSGLEGSIQTDLSLETIMS
LVNTQLESGTQFTVESQALTGTGRSDLSSYAMPGSQLYMMEINQDSLEQSKAAIQSVLVE
K

Fig. 3 cont. CPS2A

SEQ. ID. NO. 12

change margins

MNNQEVNAIEIDVLFLLKTIWRKKFLILLTAVLTAGLAFVYSSFLVTPQYDSTTRIYVVS
QNVEAGAGLTNQELQAGTYLAKDYREIILSQDVLTQVATELNLKESLKEKISVSIPVDTR
IVSISVRDADPNEAARIANSLRTFAVQKVVEVTKVSDVTTLEEAVPAEEPTTPNTKRNIL
LGLLAGGILATGLVLVMEVLDDRVKRPQDIEEVMGLTLLGIVPDSKKLK

Fig. 3 cont. CPS2B

SEQ. ID. NO. 13

revised to satisfy margin requirements

MAMLEIARTKREGVNKTEEYFNAIRTNIQLSGADIKVVGITSVKSNEGKSTTAASLAIAY
ARSGYKTVLVDADIRNSVMPGFFKPITKITGLTDYLAGTTDLSQGLCDTDIPNLTVIESG
KVSPNPTALLQSKNFENLLATLRRYYDYVIVDCPPLGLVIDAAIIAQKCDAMVAVVEAGN
VKCSSLKKVKEQLEQTGTPFLGVILNKYDIATEKYSEYGNYGKKA

Fig. 3 cont. CPS2C

SEQ. ID. NO. 14

revised to satisfy margin requirements

MIDIHSHIIFGVDDGPKTIEESLSLISEAYRQGVRYIVATSHRRKGMFETPEKIIMINFL
QLKEAVAEVYPEIRLCYGAELYYSKDILSKLEKKKVPTLNGSCYILLEFSTDTPWKEIQE
AVNEMTLLGLTPVLAHIERYDALAFQSERVEKLIDKGCYTQVNSNHVLKPALIGERAKEF
KKRTRYFLEQDLVHCVASDMHNLYSRPPFMREAYQLVKKEYGEDRAKALFKKNPLLILKN
QVQ

Fig. 3 cont. CPS2D

SEQ. ID. NO. 15

revised to satisfy margin requirements

MNIEIGYRQTKLALFDMIAVTISAILTSHIPNADLNRSGIFIIMMVHYFAFFISRMPVEF
EYRGNLIEFEKTFNYSIIFVIFLMAVSFMLENNFALSRRGAVYFTLINFVLVYLFNVIIK
QFKDSFLFSTTYQKKTILITTAELWENMQVLFESDILFQKNLVALVILGTEIDKINLPLP
LYYSVEEAIGFSTREVVDYVFINLPSEYFDLKQLVSDFELLGIDVGVDINSFGFTVLKNK
KIQMLGDHSIVTFSTNFYKPSHIWMKRLLDILGAVVGLIISGIVSILLIPIIRRDGGPAI
FAQKRVGQNGRIFTFYKFRSMFVDAEVRKKELMAQNQMQGGMFKMDNDPRITPIGHFIRK
TSLDELPQFYNVLIGDMSLVGTRPPTVDEFEKYTPSQKRRLSFKPGITGLWQVSGRSDIT
DFNEVVRLDLTYIDNWTIWSDIKILLKTVKVVLLREGGQ

Fig. 3 cont. CPS2E

SEQ. ID. NO. 16

modified to comply with margin requirements

MRTVYIIGSKGIPAKYGGFETFVEKLTEYQKDKSINYFVACTRENSAKSDITGEVFEHNG
ATCFNIDVPNIGSAKAILYDIMALKKSIEIAKDRNDTSPIFYILACRIGPFIYLFKKQIE
SIGGQLFVNPDGHEWLREKWSYPVRQYWKFSESLMLKYADLLICDSKNIEKYIHEDYRKY
APETSYIAYGTDLDKSRLSPTDSVVREWYKEKEISENDYYLVVGRFVPENNYEVMIREFM
KSYSRKDFVLITNVEHNSFYEKLKKETGFDKDKRIKFVGTVYNQELLKYIRENAFAYFHG
HEVGGTNPSLLEALSSTKLNLLLDVGFNREVGEEGAKYWNKDNLHRVIDSCEQLSQEQIN
DMDSLSTKQVKERFSWDFIVDEYEKLFKG

Fig. 3 cont. CPS2F

SEQ. ID. NO. 17

modified to comply with margin requirements

MKKILYLHAGAELYGADKVLLELIKGLDKNEFEAHVILPNDGVLVPALREVGAQVEVINY
PILRRKYFNPKGIFDYFISYHHYSKQIAQYAIENKVDIIHNNTTAVLEGIYLKRKLKLPL
LWHVHEIIVKPKFISDSINFLMGRFADKIVTVSQAVANHIKQSPHIKDDQISVIYNGVDN
KVFYQSDARSVRERFDIDEEALVIGMVGRVNAWKGQGDFLEAVAPILEQNPKAIAFIAGS
AFEGEEWRVVELEKKISQLKVSSQVXRMDYYANTTELYNMFDIFVLPSTNPDPLPTVVLK
AMACGKPVVGYRHGGVCEMVKEGVNGFLVTPNSPLNLSKVILQLSENINLRKKIGNNSIE
RQKEHFSLKSYVKNFSKVYTSLKVY

Fig. 3 cont. CPS2G

SEQ. ID. NO. 18

modified to comply with margin requirement

MKIISFTMVNNESEIIESFIRYNYNFIDEMVIIDNGCTDNTMQIIFNLIKEGYKISVYDE
SLEAYNQYRLDNKYLTKIIAEKNPDLIIPLDADEFLTADSNPRKLLEQLDLEKIHYVNWQ
WFVMTKKDDINDSFIPRRMQYCFEKPVWHHSDGKPVTKCIISAKYYKKMNLKLSMGHHTV
FGNPNVRIEHHNDLKFAHYRAISQEQLIYKTICYTIRDIATMENNIETAQRTNQMALIES
GVDMWETAREASYSGYDCNVIHAPIDLSFCKENIVIKYNELSRETVAERVMKTGREMAVR
AYNVERKQKEKKFLKPIIFVLDGLKGDEYIHPNPSNHLTILTEMYNVRGLLTDNHQIKFL
KVNYRLIITPDFAKFLPHEFIVVPDTXDIEQVKSQYVGTGVDLSKIISLKEYRKEIGFIG
NLYALLGFVPNMLNRIYLYIQRNGIANTIIKIKSRL.

Fig. 3 cont. CPS2H

SEQ. ID. NO. 19

modified to comply with margin requirement

MQADRRKTFGKMRIRINNLFFVAIAFMGIIISNSQVVLAIGKASVIQYLSYLVLILCIVN
DLLKNNKHIVVYKLGYLFLIIFLFTIGICQQILPITTKIYLSISMMIISVLATLPISLIK
DIDDFRRISNHLLFALFITSILGIKMGATMFTGAVEGIGFSQGFNGGLTHKNFFGITILM
GFVLTYLAYKYGSYKRTDRFILGLELFLILISNTRSVYLILLLFLFLVNLDKIKIEQRQW
STLKYISMLFCAIFLYYFFGFLITHSDSYAHRVNGLINFFEYYRNDWFHLMFGAADLAYG
DLTLDYAIRVRRVLGWNGTLEMPLLSIMLKNGFIGLVGYGIVLYKLYRNVRILKTDNIKT
IGKSVFIIVVLSATVENYIVNLSFVFMPICFCLLNSISTMESTINKQLQT

Fig. 3 cont. CPS2I

SEQ. ID. NO. 20

modified to comply with margin requirement

MEKVSIIVPIFNTEKYLRECLDSIISQSYTNLEILLIDDGSSDSSTDICLEYAEQDGRIK
LFRLPNGGVSNARNYGIKNSTANYIMFVDSDDIVDGNIVESLYTCLKENDSDLSGGLLAT
FDGNYQESELQKCQIDLEEIKEVRDLGNENFPNHYMSGIFNSPCCKLYKNIYINQGFDTE
QWLGEDLLFNLNYLKNIKKVRYVNRNLYFARRSLQSTTNTFKYDVFIQLENLEEKTFDLF
VKIFGGQYEFSVFKETLQWHIIYYSLLMFKNGDESLPKKLHIFKYLYNRHSLDTLSIKRT
SSVFKRICKLIVANNLFKIFLNTLIREEKNND

Fig. 3 cont. CPS2J

SEQ. ID. NO. 21

modified comply with margin requirement

MINISIIVPI YNVEQYLSKC INSIVNQTYK HIEILLVNDG STDNSEEICL AYAKKDSRIR
YFKKENGGLS DARNYGISRA KGDYLAFIDS DDFIHSEFIQ RLHEAIEREN
ALVAVAGYDR VDASGHFLTA EPLPTNQAVL SGRNVCKKLL EADGHRFVVA WNKLYKKELF
EDFRFEKGKI HEDEYFTYRL LYELEKVAIV KECLYYYVDR ENSIITSSMT
DHRFHCLLEF QNERMDFYES RGDKELLLEC YRSFLAFAVL FLGKYNHWLS KQQKKLLQTL
FRIVYKQLKQ NKRLALLMNA YYLVGCLHLN FSVFLKTGKD KIQERLRRSE
SSTR

Fig. 3 cont. CPS2K

SEQ. ID. NO. 22

modification to comply with margin requirement

MSKKSIVVSG LVYTIGTILV QGLAFITLPI YTRVISQEVY GQFSLYNSWV GLVGLFIGLQ
LGGAFGPGWV HFREKFDDFV STLMVSSIAF FLPIFGLSFL LSQPLSLLFG
LPDWVVPLIF LQSLMIVVQG FFTTYLVQRQ QSMWTLPLSV LSAVINTALS LFLTFPMEND
FIARVMANPA TTGVLACVSX WFSQKKNGLH FRKDYLRYGL SISIPLIFHG
LGHNVLNQFD RIMLGKMLTL SDVALYSFGY TLASILQIVF SSLNTVWCPW YFEKKRGADK
DLLSYVRYYL AIGLFVTFGF LTIYPELAML LGGSEYRFSM GFIPMIIVGV
FFVFLYSFPA NIQFYSGNTK FLPIGTFIAG VLNISVHFVL IPTKNLWCCF ATTASYLLLL
VLHYFVAKKK YAYDEVAIST FVKVIALVVV YTGLMTVFVG SIWIRWSLGI
AVLVVYAYIF RKELTVALNT FREKRSK

Fig. 3 cont. CPS20

SEQ. ID. NO. 23

modified to comply with margin requirement

MVYIIAEIGC NHNGDVHLAR KMVEVAVDCG VDAVKFQTFK ADLLISKYAP KAEYQKITTG
ESDSQLEMTR RLELSFEEYL DLRDYCLEKG VDVFSTPFDE ESLDFLISTD
MPVYKIPSGE ITNLPYLEKI GRQAKKVILS TGMAVMDEIH QAVKILQENG TTDISILHCT
TEYPTPYPAL NLNVLHTLKK EFPNLTIGYS DHSVGSEVPI AAAAMGAELI
EKHFTLDNEM EGPDHKASAT PDILAALVKG VRIVEQSLGK FEKEPEEVEV RNKIVARKSI
VAKKAIAKGE VFTEENITVK RPGNGISPME WYKVLGQVSE QDFEEDQNIC
HSAFENQM

Fig. 3 cont. CPS2P

SEQ. ID. NO. 24

Change margins

MKKICFVTGS RAEYGIMRRL LSYLQDDPEM ELDLVVTAMH LEEKYGMTVK DIEADKRRIV
KRIPLHLTDT SKQTIVKSLA TLTEQLTVLF EEVQYDLVLI LGDRYEMLPV
ANAALLYNIP ICHIHGGEKT MGNFDESIRH AITKMSHLHL TSTDEFRNRV IQLGENPTMY

Fig. 3 cont. CPS2Q

SEQ. ID. NO. 25

change margins

MELGIDFAED YYVVLFHPVT LEDNTAEEQT QALLDALKED GSQCLIIGSN SDTHADKIME
LMHEFVKQDS DSYIFTSLPT RYYHSLVKHS QGLIGNSSSG LIEVPSLQVP
TLNIGNRQFG RLSGPSVVHV GTSKEAIVGG LGQLRDVIDF TNPFEQPDSA LQGYRAIKEF
LSVQASTMKE FYDR

Fig. 3 cont. CPS2R

SEQ. ID. NO. 26

Change margins

MKKVAFLGAG TFSDGVLPWL DRTRYELIGY FEDKPISDYR GYPVFGPLQD VLTYLDDGKV
DAVFVTIGDN VKRKEIFDLL AKDHYDALFN IISEQANIFS PDSIKGRGVF
IGFSSFVGAD SYVYDNCIIN TGAIVEHHTT VEAHCNITPG VTINGLCRIG ESTYIGSGST
VIQCIEIAPY TTLGAGTVVL KSLTESGTYV GVPARKIK

Fig. 3 cont. CPS2S

SEQ. ID. NO. 27

Change Margins

MEPICLIPAR SGSKGLPNKN MLFLDGVPMI FHTIRAAIES GCFKKENIYV STDSEVYKEI
CETTGVQVLM RPADLATDFT TSFQLNEHFL QDFSDDQVFV LLQVTSPLRS
GKHVKEAMEL YGKGQADHVV SFTKVDKSPT LFSTLDENGF AKDIAGLGGS YRRQDEKTLY
YPNGAIYISS KQAYLADKTY FSEKTAAYVM TKEDSIDVDD HFDFTGVIGR
IYFDYQRREQ QNKPFYKREL KRLCEQRVHD SLVIGDSRLL ALLLDGFDNI SIGGMTASTA
LENQGLFLAT PIKKVLLSLG VNDLITDYPL HMIEDTIRQL MESLVSKAEQ
VFVTTIAYTL FRDSVSNEEI VQLNDVIVQS ASELGISVID LNEVVEKEAM LDYQYTNDGL
HFNQIGQERV NQLILTSLTR

Fig. 3 cont. CPS2T

SEQ. ID. NO. 28

change margins

ATCGCCAAAC GAAATTGGCA TTATTTGATA TGATAGCAGT TGCAATTTCT GCAATCTTAA CAAGTCATAT
ACCAAATGCT GATTTAAATC GTTCTGGAAT TTTTATCATA
ATGATGGTTC ATTATTTTGC ATTTTTTATA TCTCGTATGC CAGTTGAATT TGAGTATAGA GGTAATCTGA
TAGAGTTTGA AAAAACATTT AACTATAGTA TAATATTTGC
AATTTTTCTT ACGGCAGTAT CATTTTTGTT GGAGAATAAT TTCGCACTTT CAAGACGTGG TGCCGTGTAT
TTCACATTAA TAAACTTCGT TTTGGTATAC CTATTTAACG
TAATTATTAA GCAGTTTAAG GATAGCTTTC TATTTTCGAC AATCTATCAA AAAAAGACGA TTCTAATTAC
AACGGCTGAA CGATGGGAAA ATATGCAAGT TTTATTTGAA
TCACATAAAC AAATTCAAAA AAATCTTGTT GCATTGGTAG TTTTAGGTAC AGAAATAGAT AAAATTAATT
TATCATTACC GCTCTATTAT TCTGTGGAAG AAGCTATAGA
GTTTTCAACA AGGGAAGTGG TCGACCACGT CTTTATAAAT CTACCAAGTG AGTTTTTAGA CGTAAAGCAA
TTCGTTTCAG ATTTTGAGTT GTTAGGTATT GATGTAAGCG
TTGATATTAA TTCATTCGGT TTTACTGCGT TGAAAAACAA AAAAATCCAA CTGCTAGGTG ACCATAGCAT
TGTAACTTTT TCCACAAATT TTTATAAGCC TAGTCATATC
ATGATGAAAC GACTTTTGGA TATACTCGGA GCGGTAGTCG GGTTAATTAT TTGTGGTATA GTTTCTATTT
TGTTAGTTCC AATTATTCGT AGAGATGGTG GACCGGCTAT
TTTTGCTCAG AAACGAGTTG GACAGAATGG ACGCATATTT ACATTCTACA AGTTTCGATC GATGTATGTT
GATGCTGAGG AGCGCAAAAA AGACTTGCTC AGCCAAAACC
AGATGCAAGG GTGGGTATGT TTTAAAATGG GAAAAACGAT CCTAGAATTA CTCCAATTGG ACATTTCATA
CGCAAAAACA AGTTTAGACG AGTTACCACA GTTTTATAAT
GTTTTAATTG GCGATATGAG TCTAGTTGGT ACACGTCCAC CTACAGTTGA TGAATTTGAA AAATATACTC
CTGGTCAAAA GAGACGATTG AGTTTTAAAC CAGGGATTAC
AGGTCTCTGG CAGGTTAGTG GTCGTAGTAA TATCACAGAC TTCGACGACG TAGTTCGGTT GGACTTAGCA
TACATTGATA ATTGGACTAT CTGGTCAGAT ATTAAAATTT
TATTAAAGAC AGTGAAAGTT GTATTGTTGA GAGAGGGAAG TAAGTAAAAG TATATGAAAG TTTGTTTGGT
CGGTTCTTCA GGGGGACATT TGACTCACTT GTATTTGTTA
AAACCGTTTT GGAAGGAAGA AGAACGTTTT TGGGTAACAT TTGATAAAGA GGATGCAAGA AGTCTTTTGA
AGAATGAAAA AATGTATCCA TGTTACTTTC CAACAAATCG
CAATCTCATT AATTTAGTGA AAAATACTTT CTTAGCTTTC AAAATTTTAC GTGATGAGAA ACCAGATGTT
ATTATTTCAT CTGGTGCGGC CGTTGCTGTC CCCTTCTTTT
ACATCGGAAA ACTATTTGGA GCAAAGACGA TTTATATTGA AGTATTTGAT CGAGTTAATA AATCTACATT
AACTGGAAAA CTAGTTTATC CCGTAACAGA TATTTTTATT
GTTCAGTGGG AAGAAATGAA GAAGGTATAT CCTAAATCTA TTAACTTGGG GAGTATTTTT TAATGATTTT
TGTAACAGTA GGAACTCATG AACAACAGTT TAATCGATTG
ATAAAAGAGA TTGATTTATT GAAAAAAAAT GGAAGTATAA CCGACGAAAT ATTTATTCAA ACAGGATATT
CTGACTATAT TCCAGAATAT TGCAAGTATA AAAAATTTCT
CAGTTACAAA GAAATGGAAC AATATATTAA CAAATCAGAA GTAGTTATTT GCCACGGAGG CCCCGCTACT
TTTATGAATT CATTATCCAA AGGAAAAAAA CAATTATTGT
TTCCTAGACA AAAAAAGTAT GGTGAACATG TAAATGATCA TCAAGTAGAG TTTGTAAGAA GAATTTTACA
AGATAATAAT ATTTTATTTA TAGAAAATAT AGATGATTTG
TTTGAAAAAA TTATTGAAGT TTCTAAGCAA ACTAACTTTA CATCAAATAA TAATTTTTTT TGTGAAAGAT
TAAAACAAAT AGTTGAAAAA TTTAATGAGG ATCAAGAAAA
TGAATAATAA AAAAGATGCA TATTTGATAA TGGCTTATCA TAATTTTTCT CAGATTTTAC TGGAGAGGGA
TACAGATATT ATCATCTTCT CTCAGGAGAA TGCACACCAT
TAGTTCCTTC AGAATACCTG TATAATTATT TTAAATATTC TCAGGATTTA TATGTTGAAT TTACAAAAGA
TGAGCAAAAA TATAAAGAAA ATAGGATATA TGAACGAGTT
AAATGTTACA GATTATTTCC TAATATATCA GAAAAAACTA TTGATAATGT ACTGTTTAGA ATTTTATTAA
GAATGTATCG AGCTTTTGAA TACTATTTAC AAAGATTGTT
GTTTATTGAT AGAATAAAAA ACATGGTCTA AGAATAAGAT TTGGTTCTAA TTGGGTTTCG CTTCCACATG
ATTTTGTGGC AATTCTTTTA TCAAATGAAA ACGAAACAGC
TTATTTATTT AAGTAATCTA AATGTCCAGA TGAACTATTT ATACAGACAA TTATAGAAAA ATATGAATTT
TCAAATAGAT TATCTAAATA TGGAAATTTA AGATATATAA
AGTGGAAAAA ATCAACATCT TCTCCTATTG TCTTTACAGA TGATTCTATT GATGAATTGC TAAATGCAAG
AAATTTAGGT TTTTTATTTG CTAGAAAGTT AAAAATAGAA
AATAAATCTA AATTTAAAGA AATTATTACT AAAAAATAAA ATAGTTGATT TTGTGAGAGT AATGTATGTT
TAAATTATTT AAATATGACC CGGAATATTT TATTTTTAAG
TACTTCTGGT TGATTATTTT TATTCCAGAG CAAAAGTATG TATTTTTATT AATTTTTATG AATTTAATTT
TATTTCATAT AAAATTTTTG AAAACTAAGC TAATATTAAA
AAATGAAATT TTATTGTTTT TATTATGGTC TATATTATGT TTTGTTTCAG TAGTCACAAG TATGTTTGTT
GAAATAAATT TTGAAAGATT ATTTGCAGAT TTTACTGCTC
CCATAATTTG GATTATTGCA ATAATGTATT ATAATTTGTA TTCATTTATA AATATTGATT ATAAAAAATT
AAAAAATAGT ATCTTTTTTA GTTTTTTAGT TTTATTAGGT
ATATCTGCAT TGTATATTAT TCAAAATGGG AAAGATATTG TATTTTTAGA CAGACACCTT ATAGGACTAG
ACTATCTTAT AACAGGCGTC AAAACAAGGT TGGTTGGCTT
TATGAACTAT CCTACGTTAA ATACCACTAC AATTATAGTT TCAATTCCGT TAATCTTTGC ACTTATAAAA
AATAAAATGC AACAATTTTT TTTCTTGTGT CTTGCTTTTA

Fig. 4

change margins

TACCGATCTA TTTAAGTGGA TCGAGAATTG GTAGTTTATC GCTAGCAATA TTAATTATAT GCTTGTTATG
GAGATATATA GGTGGAAAAT TTGCTTGGAT AAAAAAGCTA
ATAGTAATAT TTGTAATACT ACTTATTATT TTAAATACTG AATTGCTTTA CCATGAAATT TTGGCTGTTT
ATAATTCTAG AGAATCAAGT AACGAAGCTA GATTTATTAT
TTATCAAGGA AGTATTGATA AAGTATTAGA AAACAATATT TTATTTGGAT ATGGAATATC CGAATATTCA
GTTACGGGAA CTTGGCTCGG AAGTCATTCA GGCTATATAT
CATTTTTTTA TAAATCAGGA ATAGTTGGGT TGATTTTACT GATGTTTTCT TTTTTTTATG TTATAAAAAA
AAGTTATGGA GTTAATGGGG AAACAGCACT ATTTTATTTT
ACATCATTAG CCATATTTTT CATATATGAA ACAATAGATC CGATTATTAT TATATTAGTA CTATTCTTTT
CTTCAATAGG TATTTGGAAT AATATAAATT TTAAAAAGGA
TATGGAGACA AAAAATGAAT GATTTAATTT CAGTTATTGT ACCAATTTAT AATGTCCAAG ATTATCTTGA
TAAATGTATT AACAGTATTA TTAACCAAAC ATATACTAAT
TTAGAGGTTA TTCTCGTAAA TGATGGAAGT ACTGATGATT CTGAGAAAAT TTGCTTAAAC TATATGAAGA
ACGATGGAAG AATTAAATAT TACAAGAAAA TTAATGGCGG
TCTAGCAGAT GCTCGAAATT TCGGACTAGA ACATGCAACA GGTAAATATA TTGCTTTTGT CGATTCTGAT
GACTATATAG AAGTTGCAAT GTTCGAGAGA ATGCATGATA
ATATAACTGA GTATAATGCC GATATAGCAG AGATAGATTT TTGTTTAGTA GACGAAAACG GGTATACAAA
GAAAAAAAGA AATAGTAATT TTCATGTCTT AACGAGAGAA
GAGACTGTAA AAGAATTTTT GTCAGGATCT AATATAGAAA ATAATGTTTG GTGCAAGCTT TATTCACGAG
ATATTATAAA AGATATAAAA TTCCAAATTA ATAATAGAAG
TATTGGTGAG GATTTGCTTT TTAATTTGGA GGTCTTGAAC AATGTAACAC GTGTAGTAGT TGATACTAGA
GAATATTATT ATAATTATGT CATTCGTAAC AGTTCGCTTA
TTAATCAGAA ATTCTCTATA AATAATATTG ATTTAGTCAC AAGATTGGAG AATTACCCCT TTAAGTTAAA
AAGAGAGTTT AGTCATTATT TTGATGCAAA AGTTATTAAA
GAGAAGGTTA AATGTTTAAA CAAAATGTAT TCAACAGATT GTTTGGATAA TGAGTTCTTG CCAATATTAG
AGTCTTATCG AAAAGAAATA CGTAGATATC CATTTATTAA
AGCGAAAAGA TATTTATCAA GAAAGCATTT AGTTACGTTG TATTTGATGA AATTTTCGCC TAAACTATAT
GTAATGTTAT ATAAGAAATT TCAAAAGCAG TAGAGGTAAA
AATGGATAAA ATTAGTGTTA TTGTTCCAGT TTATAATGTA GATAAATATT TAAGTAGTTG TATAGAAAGC
ATTATTAATC AAAATTATAA AAATATAGAA ATATTATTGA
TAGATGATGG CTCTGTAGAT GATTCTGCTA AAATATGCAA GGAATATGCA GAAAAAGATA AAAGAGTAAA
AATTTTTTTC ACTAATCATA GTGGAGTATC AAATGCTAGA
AATCATGGAA TAAAGCGGAG TACAGCTGAA TATATTATGT TTGTTGACTC TGATGATGTT GTTGATAGTA
GATTAGTAGA AAAATTATAT TTTAATATTA TAAAAAGTAG
AAGTGATTTA TCTGGTTGTT TGTACGCTAC TTTTTCAGAA AATATAAATA ATTTTGAAGT GAATAATCCA
AATATTGATT TTGAAGCAAT TAATACCGTG CAGGACATGG
GAGAAAAAAA TTTTATGAAT TTGTATATAA ATAATATTTT TTCTACTCCT GTTTGTAAAC TATATAAGAA
AAGATACATA ACAGATCTTT TTCAAGAGAA TCAATGGTTA
GGAGAAGATT TACTTTTTAA TCTGCATTAT TTAAAGAATA TAGATAGAGT TAGTTATTTG ACTGAACATC
TTTATTTTTA TAGGAGAGGT ATACTAAGTA CAGTAAATTC
TTTTAAAGAA GGTGTGTTTT TGCAATTGGA AAATTTGCAA AAACAAGTGA TAGTATTGTT TAAGCAAATA
TATGGTGAGG ATTTTGACGT ATCAATTGTT AAAGATACTA
TACGTTGGCA AGTATTTTAT TATAGCTTAC TAATGTTTAA ATACGGAAAA CAGTCTATTT TTGACAAATT
TTTAATTTTT AGAAATCTTT ATAAAAAATA TTATTTTAAC
TTGTTAAAAG TATCTAACAA AAATTCTTTG TCTAAAAATT TTTGTATAAG AATTGTTTCG AACAAAGTTT
TTAAAAAAAT ATTATGGTTA TAATAGGAAG ATATCATGGA
TACTATTAGT AAAATTTCTA TAATTGTACC TATATATAAT GTAGAAAAAT ATTTATCTAA ATGTATAGAT
AGCATTGTAA ATCAGACCTA CAAACATATA GAGATTCTTC
TGGTGAATGA CGGTAGTACG GATAATTCGG AAGAAATTTG TTTAGCATAT GCGAAGAAAG ATAGTCGCAT
TCGTTATTTT AAAAAAGAGA ACGGCGGGCT ATCAGATGCC
CGTAATTATG GCATAAGTCG CGCCAAGGGT GACTACTTAG CTTTTATAGA CTCAGATGAT TTTATTCATT
CGGAGTTCAT CCAACGTTTA CACGAAGCAA TTGAGAGAGA
GAATGCCCTT GTGGCAGTTG CTGGTTATGA TAGGGTAGAT GCTTCGGGGC ATTTCTTAAC AGCAGAGCCG
CTTCCTACAA ATCAGGCTGT TCTGAGCGGC AGGAATGTTT
GTAAAAAGCT GCTAGAGGCG GATGGTCATC GCTTTGTGGT GGCCTGTAAT AAACTCTATA AAAAAGAACT
ATTTGAAGAT TTTCGATTTG AAAAGGGTAA GATTCATGAA
GATGAATACT TCACTTATCG CTTGCTCTAT GAGTTAGAAA AAGTTGCAAT AGTTAAGGAG TGCTTGTACT
ATTATGTTGA CCGAGAAAAT AGTATCACAA CTTCTAGCAT
GACTGACCAT CGCTTCCATT GCCTACTGGA ATTTCAAAAT GAACGAATGG ACTTCTATGA AAGTAGAGGA
GATAAAGAGC TCTTACTAGA GTGTTATCGT TCATTTTTAG
CCTTTGCTGT TTTGTTTTTA GGCAAATATA ATCATTGGTT GAGCAAACAG CAAAAGAAGC TT

Fig. 4 cont.

SEQ. ID. NO. 29

RQTKLALFDM IAVAISAILT SHIPNADLNR SGIFIIMMVH YFAFFISRMP VEFEYRGNLI
EFEKTFNYSI IFAIFLTAVS FLLENNFALS RRGAVYFTLI NFVLVYLFNV
IIKQFKDSFL FSTIYQKKTI LITTAERWEN MQVLFESHKQ IQKNLVALVV LGTEIDKINL
SLPLYYSVEE AIEFSTREVV DHVFINLPSE FLDVKQFVSD FELLGIDVSV
DINSFGFTAL KNKKIQLLGD HSIVTFSTNF YKPSHIMMKR LLDILGAVVG LIICGIVSIL
LVPIIRRDGG PAIFAQKRVG QNGRIFTFYK FRSMYVDAEE RKKDLLSQNQ
MQGWVCFKMG KTILELLQLD ISYAKTSLDE LPQFYNVLIG DMSLVGTRPP TVDEFEKYTP
GQKRRLSFKP GITGLWQVSG RSNITDFDDV VRLDLAYIDN WTIWSDIKIL
LKTVKVVLLR EGSK

Fig. 4 cont. CPS1E

SEQ. ID. NO. 30

Modify margins

MKVCLVGSSG GHLTHLYLLK PFWKEEERFW VTFDKEDARS LLKNEKMYPC YFPTNRNLIN
LVKNTFLAFK ILRDEKPDVI ISSGAAVAVP FFYIGKLFGA KTIYIEVFDR
VNKSTLTGKL VYPVTDIFIV QWEEMKKVYP KSINLGSIF

Fig. 4 cont. CPS1F

SEQ. ID. NO. 31

modify margins

MIFVTVGTHE QQFNRLIKEI DLLKKNGSIT DEIFIQTGYS DYIPEYCKYK KFLSYKEMEQ
YINKSEVVIC HGGPATFMNS LSKGKKQLLF PRQKKYGEHV NDHQVEFVRR
ILQDNNILFI ENIDDLFEKI IEVSKQTNFT SNNNFFCERL KQIVEKFNED QENE

Fig. 4 cont. CPS1G

SEQ. ID. NO. 32

Moleby Margins

MFKLFKYDPE YFIFKYFWLI IFIPEQKYVF LLIFMNLILF HIKFLKTKLI LKNEILLFLL
WSILCFVSVV TSMFVEINFE RLFADFTAPI IWIIAIMYYN LYSFINIDYK
KLKNSIFFSF LVLLGISALY IIQNGKDIVF LDRHLIGLDY LITGVKTRLV GFMNYPTLNT
TTIIVSIPLI FALIKNKMQQ FFFLCLAFIP IYLSGSRIGS LSPLAILIIC
LLWRYIGGKF AWIKKLIVIF VILLIILNTE LLYHEILAVY NSRESSNEAR FIIYQGSIDK
VLENNILFGY GISEYSVTGT WLGSHSGYIS FFYKSGIVGL ILLMFSFFYV
IKKSYGVNGE TALFYFTSLA IFFIYETIDP IIIILVLFFS SIGIWNNINF KKDMETKNE

Fig. 4 cont. CPS1H

SEQ. ID. NO. 33

modify margins

MNDLISVIVP IYNVQDYLDK CINSIINQTY TNLEVILVND GSTDDSEKIC LNYMKNDGRI
KYYKKINGGL ADARNFGLEH ATGKYIAFVD SDDYIEVAMF ERMHDNITEY
NADIAEIDFC LVDENGYTKK KRNSNFHVLT REETVKEFLS GSNIENNVWC KLYSRDIIKD
IKFQINNRSI GEDLLFNLEV LNNVTRVVVD TREYYYNYVI RNSSLINQKF
SINNIDLVTR LENYPFKLKR EFSHYFDAKV IKEKVKCLNK MYSTDCLDNE FLPILESYRK
EIRRYPFIKA KRYLSRKHLV TLYLMKFSPK LYVMLYKKFQ KQ

Fig. 4 cont. CPS1I

SEQ. ID. NO. 34

modify margins

MDKISVIVPV YNVDKYLSSC IESIINQNYK NIEILLIDDG SVDDSAKICK EYEKDKRVKI
FFTNHSGVSN ARNHGIKRST AEYIMFVDSD DVVDSRLVEK LYFNIIKSRS
DLSGCLYATF SENINNFEVN NPNIDFEAIN TVQDMGEKNF MNLXXNNIFS TPVCXLYQKR
YITDLFQENQ WLGEDLLFNL HYLKNIDRVS YLTEHLYFYR RGILSTVNSF
KEGVFLQLEN LQKQVIVLFK QIYGEDFDVS IVKDTIRWQV FYYSLLMFKY GKQSIFDKFL
IFRNLYKKYY FNLLKVSNKN SLSKNFCIRI VSNKVFKKIL WL

Fig. 4 cont. CPS1J

SEQ. ID. NO. 35

modify margins

MDTISKISII VPIYNVEKYL SKCIDSIVNQ TYKHIEILLV NDGSTDNSEE ICLAYAKKDS
RIRYFKKENG GLSDARNYGI SRAKGDYLAF IDSDDFIHSE FIQRLHEAIE
RENALVAVAG YDRVDASGHF LTAEPLPTNQ AVLSGRNVCK KLLEADGHRF VVACNKLYKK
ELFEDFRFEK GKIHEDEYFT YRLLYELEKV AIVKECLYYY VDRENSITTS
SMTDHRFHCL LEFQNERMDF YESRGDKELL LECYRSFLAF AVLFLGKYNH WLSKQQKK

Fig. 4 cont. CPS1K

SEQ. ID. NO. 36

modify margins

AAGCTTATCG TCAAGGTGTT CGCTATATCG TGGCGACATC TCATAGACGA AAAGGGATGT
TTGAAACACC AGAAAAAGTT ATCATGACTA ACTTTCTTCA ATTTAAAGAC
GCAGTAGCAG AAGTTTATCC TGAAATACGA TTGTGCTATG GTGCTGAATT GTATTATAGT
AAAGATATAT TAAGCAAACT TGAAAAAAAG AAAGTACCCA CACTTAATGG
CTCGCGCTAT ATTCTTTTGG AGTTCAGTAG TGATACTCCT TGGAAAGAGA TTCAAGAAGC
AGTGAACGAA GTGACGCTAC TTGGGCTAAC TCCCGTACTT GCCCATATAG
AACGATATGA CGCCCTAGCG TTTCATGCAG AGAGAGTAGA AGAGTTAATT GACAAGGGAT
GCTATACTCA GGTAAATAGT AATCATGTGC TGAAGCCCAC TTTAATTGGT
GATCGAGCAA AAGAATTTAA AAAACGTACT CGGTATTTTT TAGAGCAGGA TTTAGTACAT
TGTGTTGCTA GCGATATGCA TAATTTATCT AGTAGACCTC CGTTTATGAG
GGAGGCTTAT AAGTTGCTAA CAGAGGAATT TGGCAAAGAT AAAGCGAAAG CGTTGCTAAA
AAAGAATCCT CTTATGCTAT TAAAAAACCA GGCGATTTAA ACTGGTTACT
CTAGATTGTG GAGAGAAAAA TGGATTTAGG AACTGTTACT GATAAACTGT TAGAACGCAA
CAGTAAACGA TTGATACTCG TGTGCATGGA TACGTGTCTT CTTATAGTTT
CCATGATTTT GAGCAGACTG TTTTTGGATG TTATTATTGA CATACCAGAT GAACGCTTCA
TTCTTGCAGT TTTATTCGTA TCAATTTTAT ATTTGATTCT ATCGTTTAGA
TTAAAAGTCT TTTCATTAAT TACGCGTTAC ACAGGGTATC AGAGTTATGT AAAAATAGGA
CTTAGTTTAA TATCTGCGCA TTCATTGTTT TTAATTATCT CAATGGTGTT
GTGGCAGGCT TTTAGTTATC GTTTCATCTT AGTATCCTTA TTTTTGTCGT ATGTAATGCT
CATTACTCCG AGGATTGTTT GGAAAGTCTT ACATGAGACG AGAAAAAATG
CTATCCGTAA GAAGGATAGC CCACTAAGAA TCTTAGTAGT AGGTGCTGGA GATGGTGGTA
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GGTATCGTTG ATCGTGATCC AAATAAACTT GGAACATTTA TCCGTACGGC TAAAGTTTTA
GGAAACCGTA ATGATATTCC ACGACTGGTA GAGGAATTAG CTGTTGACCA
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AATATCAACC CGATGTTGTT TATCATGCTG CAGCACATAA GCATGTTCCT TTGATGGAAT
ATAATCCACA TGAAGCAGTG AAGAATAATA TTTTTGGAAC GAAGAATGTG
GCTGAGGCGG CTAAAACTGC AAAGGTTGCC AAATTTGTTA TGGTTTCAAC AGATAAAGCT
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AGGTGGAACA GGGCAGAAAG GAAAAGGATG AAATTTTCAG TATTAATGTC
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TAGCCTTGGA AAAGAATTCG GGTTTAGGAA TTGCACTGAA TGAAGGTTTG
AAACATTGTA ATTATGAGTG GGTTTGCACG AAATGGATTC TGATGATGTT GCATATACAT
ACACGTTTTG AAAAGCAAGT TAACTTTATA AAACAAAACC CGACTATAGA

modify margins

TATTGAGATA GATGAGTTCT TAAATTCTAC TAGTGAAATA GTTTCTCATA AAAATGTTCC
AACCCAGCAC GATGAAATAT TAAAGATGGC AAGGCGGGAG AAATCCATGT
GCCACATGAC TGTAATGTTT AAAAAGAAAA GTGTCGAGAG AGCAGGGGGG TATCAAACAC
TTCCGTACGT AGAAGATTAT TTCCTTTGGG TGCGCATGAT TGCTTCAGGA
TCGAAATTTG CAAACATTGA TGAAACACTA GTTCTTGCAC GTGTTGGAAA TGGGATGTTC
AATAGGAGGG GGAACAGAGA ACAAATTAAC AGTTGGACAT TACTAATTGA
ATTTATGTTA GCTCAAGGAA TTGTTACACC ACTAGATGTA TTTATTAATC AAATTTACAT
TAGGGTCTTT GTTTATATGC CAACTTGGAT AAAGAAACTC ATTTATGGAA
AAATCTTAAG GAAATAGTAT GATTACAGTA TTGATGGCTA CATATAATGG AAGCCCATTT
ATAATAAAAC AGTTAGATTC AATTCGAAAT CAAAGTGTAT CAGCAGACAA
AGTTATTATT TGGGATGATT GCTCGACAGA TGATACAATA AAAATAATAA AAGATTATAT
AAAAAAATAT TCTTTGGATT CATGGGTTGT CTCTCAAAAT AAATCTAATC
AGGGGCATTA TCAAACATTT ATAAATTTGA CAAAGTTAGT TCAGGAAGGA ATAGTCTTTT
TTTCAGATCA AGATGATATT TGGGACTGTC ATAAAATTGA GACAATGCTT
CCAATCTTTG ACAGAGAAAA TGTATCAATG GTGTTTTGCA AATCCAGATT GATTGATGAA
AACGGAAATA TTATCAGTAG CCCAGATACT TCGGATAGAA TCAATACGTA
CTCTCTAGA

Fig. 5 cont.

SEQ. ID. NO. 37

modify margins

AYRQGVRYIV ATSHRRKGMF ETPEKVIMTN FLQFKDAVAE VYPEIRLCYG AELYYSKDIL
SKLEKKKVPT LNGSRYILLE FSSDTPWKEI QEAVNEVTLL GLTPVLAHIE
RYDALAFHAE RVEELIDKGC YTQVNSNHVL KPTLIGDRAK EFKKRTRYFL EQDLVHCVAS
DMHNLSSRPP FMREAYKLLT EEFGKDKAKA LLKKNPLMLL KNQAI

Fig. 5 cont. CPS9D

SEQ. ID. NO. 38

modify margins

MDLGTVTDKL LERNSKRLIL VCMDTCLLIV SMILSRLFLD VIIDIPDERF ILAVLFVSIL
YLILSFRLKV FSLITRYTGY QSYVKIGLSL ISAHSLFLII SMVLWQAFSY
RFILVSLFLS YVMLITPRIV WKVLHETRKN AIRKKDSPLR ILVVGAGDGG NIFINTVKDR
KLNFEIVGIV DRDPNKLGTF IRTAKVLGNR NDIPRLVEEL AVDQVTIAIP
SLNGKEREKI VEICNTTGVT VNNMPSIEDI MAGNMSVSAF QEIDVADLLG RPEVVLDQDE
LNQFFQGKTI LVTGAGGSIG SELCRQIAKF TPKRLLLLGH GENSIYLIHR
ELLEKYQGKI ELVPLIADIQ DRELIFSIMA EYQPDVVYHA AAHKHVPLME YNPHEAVKNN
IFGTKNVAEA AKTAKVAKFV MVSTDKAVNP PNVMGATKRV AEMIVTGLNE
PGQTQFAAVR FGNVLGSRGS VVPLFKEQIR KGGPVTVTDF RMTRYFMTIP EASRLVIQAG
HLAKGGEIFV LDMGEPVQIL ELARKVILLS GHTEEEIGIV ESGIRPGEKL
YEELLSTEER VSEQIHEKIF VGRVTNKQSD IVNSFINGLL QKDRNELKNM LIEFAKQE

Fig. 5 cont. CPS9E

SEQ. ID. NO. 39

modify margins

MYPICKRILA IIISGIAIVV LSPILLLIAL AIKLDSKGPV LFKQKRVGKN KSYFMIYKFR
SMYVDAPSDM PTHLLKDPKA MITKVGAFLR KTSLDELPQL FNIFKGEMAI
VGPRPALWNQ YDLIEERDKY GANDIRPGLT GWAQINGRDE LEIDEKSKLD GYYVQNMSLG
LDIKCFLGTF LSVARSEGVV EGGTGQKGKG

Fig. 5 cont. CPS9F

SEQ. ID. NO. 40

Modify margins

MKFSVLMSVY EKEKPEFLRE SLESILVNQT MIPTEVVLVE DGPLNQSLYS ILEEFKSRFS
FFKTIALEKN SGLGIALNEG LKHCNYEWVC TKWILMMLHI HTRFEKQVNF
IKQNPTIDIE IDEFLNSTSE IVSHKNVPTQ HDEILKMARR EKSMCHMTVM FKKKSVERAG
GYQTLPYVED YFLWVRMIAS GSKFANIDET LVLARVGNGM FNRRGNREQI
NSWTLLIEFM LAQGIVTPLD VFINQIYIRV FVYMPTWIKK LIYGKILRK

Fig. 5 cont. CPS9G

SEQ. ID. NO. 41

modify margins

MITVLMATYN GSPFIIKQLD SIRNQSVSAD KVIIWDDCST DDTIKIIKDY IKKYSLDSWV
VSQNKSNQGH YQTFINLTKL VQEGIVFFSD QDDIWDCHKI ETMLPIFDRE
NVSMVFCKSR LIDENGNIIS SPDTSDRINT YSL

Fig. 5 cont. CPS9H

SEQ. ID. NO. 42

modify margins

CTGCAGCACA TAAGCATGTT CCATTGATGG AATATAATCC ACATGAAGCA GTGAAGAATA
ATATTTTTGG AACGAAGAAT GTGGCTGAGG CGGCTAAAAC TGCAAAGGTT
GCCAAATTTG TTATGGTTTC AACAGATAAA GCTGTTAATC CGCCAAATGT CATGGGAGCG
ACTAAACGTG TTGCAGAAAT GATTGTAACA GGTTTAAACG AGCCAGGTCA
GACTCAATTT GCGGCAGTCC GTTTTGGGAA TGTTCTAGGT AGTCGTGGAA GTGTTGTTCC
GCTATTCAAA GAGCAAATTA GAAAAGGTGG ACCTGTTACG GTTACCGACT
TTAGGATGAC TCGTTATTTC ATGACGATTC CTGAGGCAAG TCGTTTGGTT ATCCAAGCTG
GACATTTGGC AAAAGGTGGA GAAATCTTTG TCTTGGATAT GGGTGAGCCA
GTACAAATCC TGGAATTGGC AAGAAAAGTT ATCTTGTTAA GCGGACATAC AGAGGAAGAA
ATCGGGATTG TAGAATCTGG AATCAGACCA GGCGAGAAAC TCTACGAGGA
ATTGTTATCA ACAGAAGAAC GTGTCAGCGA ACAGATTCAT GAAAAAATAT TTGTGGGTCG
CGTTACAAAT AAGCAGTCGG ACATTGTCAA TTCATTTATC AATGGATTAC
TCCAAAAAGA TAGAAATGAA TTAAAAGATA TGTTGATTGA ATTTGCAAAA CAAGAATAAG
AAAGTAAAAA ATATTTTTAC TTTCCTAGAG TTTAAACGAT GTTTAAGTTC
TAGGAAGGTT GGAATTGCTT TCGTGGAGGT GATAGATAGA AACCTATATA TTTGTAGAAG
AAAGGATATT AAACTAAAGG TGAATCGGAA CATAAAGTTT AGATAGAGTT
GGTATTTAAT GCCAAACAGG TGAATGCAAC CTCTCGCTCG TTACTAAGCA GGAGATAGTA
AAGTTGCTTG AAAGAGAGTT TGTTAATCAG TATAAGTAGG CTAAAGTGAG
AATATATATC TATTATTATC GGTAATGATA CTATTATTGA GAATTATTGT AGTGGGGATA
AAAATAATTT TTGGTGATTT TATCGTCCGA CTTAAAGGTG GGTTAAAAAA
GTACTTATAT TCTTTTAGAA TTGATGAAAA ATATGGGGGA ATATAATATT TATAGGAGAT
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AGCAACCAGT AAATATTTTC AGAAGATAGA ATCAAGAAGA GGTGAATTAT TTATTAAATT
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TTACCAGAAA AAATGAAGTA CAATTTGGAA TATATCAGAA ACTTTGGAAT TATTTCTGAT
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TGAAGTCATT CAAAAAATGG CTGAAGCAGG TATTGCGTGC AATGTTCACT ACAAACCATT
ACCTCTTCTC ACAGCCTACA AGAATCTTGG TTTTGAAATG AAAGATTTTC
CGAATGCCTA TCAGTATTTT GAAAATGAAG TTACACTGCC TCTTCATACC AACTTGAGTG
ATGAAGATGT GGAGTATGTG ATAGAAATGT TTTTAAAAAT TGTTAGTAGA
GATTAGTTAT TTTGGAAGGA GATATGGTGG AAAGAGATAT GGTGGAAAGA GACACGTTGG
TATCTATAAT AATGCCCTCG TGGAATACAG CTAAGTATAT ATCTGAATCA
ATCCAGTCAG TGTTGGACCA AACACACCAA AATTGGGAAC TTATAATCGT TGATGATTGT
TCTAATGACG AAACTGAAAA AGTTGTTTCG CATTTCAAAG ATTCAAGAAT

DNA Serotype 7

Fig. 6

↑ modify margins

AAAGTTTTTT AAAAATTCGA ATAATTTAGG GGCAGCTCTA ACACGAAATA AGGCACTAAG
AAAAGCTAGA GGTAGGTGGA TTGCGTTCTT GGATTCAGAT GATTTATGGC
ACCCGAGTAA GCTAGAAAAA CAGCTTGAAT TTATGAAAAA TAATGGATAT TCATTTACTT
ATCACAATTT TGAAAAGATT GATGAATCTA GTCAGTCTTT ACGTGTCCTG
GTGTCAGGAC CAGCAATTGT GACTAGAAAA ATGATGTACA ATTACGGCTA TCCAGGGTGT
TTGACTTTCA TGTATGATGC AGACAAAATG GGTTTAATTC AGATAAAAGA
TATAAAGAAA AATAACGATT ATGCGATATT ACTTCAATTG TGTAAGAAGT ATGACTGTTA
TCTTTTAAAT GAAAGTTTAG CTTCGTATCG AATTAGAAAA AA

Fig. 6 cont.

SEQ. ID. NO. 43

modify margins

AAHKHVPLME YNPHEAVKNN IFGTKNVAEA AKTAKVAKFV MVSTDKAVNP PNVMGATKRV
AEMIVTGLNE PGQTQFAAVR FGNVLGSRGS VVPLFKEQIR KGGPVTVTDF
RMTRYFMTIP EASRLVIQAG HLAKGGEIFV LDMGEPVQIL ELARKVILLS GHTEEEIGIV
ESGIRPGEKL YEELLSTEER VSEQIHEKIF VGRVTNKQSD IVNSFINGLL
QKDRNELKDM LIEFAKQE

Fig. 6 cont. CPS7E

SEQ. ID. NO. 44

modify margins

MTRVELITRE FFKKNEATSK YFQKIESRRG ELFIKFFMDK LLALILLLLL SPVIIILAIW
IKLDSKGPIF YRQERVTRYG RIFRIFKFRT MISDADKVGS LVTVGQDNRI
TKVGHIIRKY RLDEVPQLFN VLMGDMSFVG VRPEVQKYVN QYTDEMFATL LLPAGITSPA
SIAYKDEDIV LEEYCSQGYS PDEAYVQKVL PEKMKYNLEY IRNFGIISDF
KVMIDTVIKV IK

Fig. 6 cont. CPS7F

SEQ. ID. NO. 45

modify margins

MTKRQNIPFS PPDITQAEID EVIDTLKSGW ITTGPKTKEL ERRLSVFTGT NKTVCLNSAT
AGLELVLRIL GVGPGDEVIV PAMTYTASCS VITHVGATPV MVDIQKNSFE
MEYDALEKAI TPKTKVIIPV DLAGIPCDYD KIYTIVENKR SLYVASDNKW QKLFGRVIIL
SDSAHSLGAS YKGKPAGSLA DFTSFSFHAV KNFTTAEGGS VTWRSHPDLD
DEEMYKEFQI YSLHGQTKDA LAKTQLGSWE YDIVIPGYKC NMTDIMAGIG LVQLERYPSL
LNRRREIIEK YNAGFEGTSI KPLVHLTEDK QSSMHLYITH LQGYTLEQRN
EVIQKMAEAG IACNVHYKPL PLLTAYKNLG FEMKDFPNAY QYFENEVTLP LHTNLSDEDV
EYVIEMFLKI VSRD

Fig. 6 cont. CPS7G

SEQ. ID. NO. 46

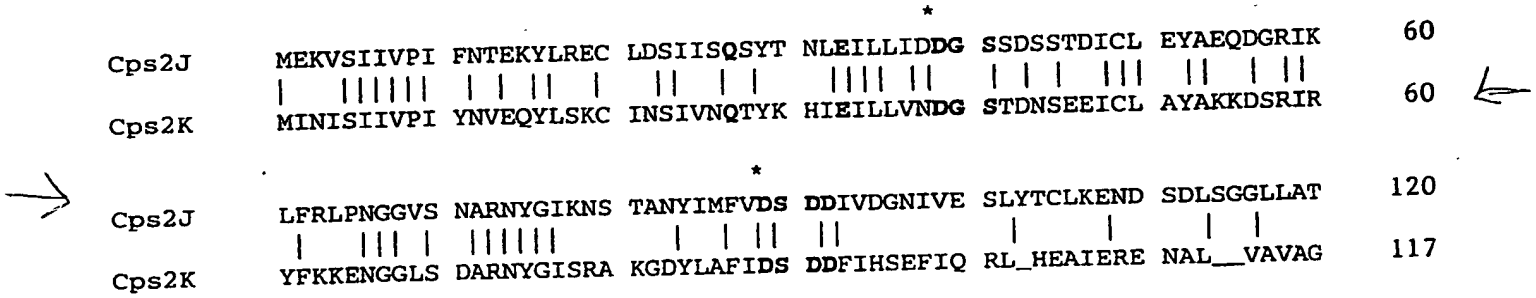
modify margins

MVERDMVERD TLVSIIMPSW NTAKYISESI QSVLDQTHQN WELIIVDDCS NDETEKVVSH
FKDSRIKFFK NSNNLGAALT RNKALRKARG RWIAFLDSDD LWHPSKLEKQ
LEFMKNNGYS FTYHNFEKID ESSQSLRVLV SGPAIVTRKM MYNYGYPGCL TFMYDADKMG
LIQIKDIKKN NDYAILLQLC KKYDCYLLNE SLASYRIRK

Fig. 6 cont. CPS7H

SEQ. ID. NO. 47

modify margins

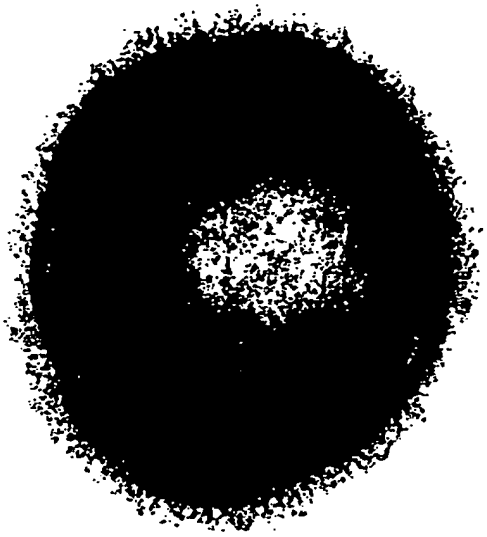


Cps2J
(SEQ. ID. NO. 51)

Fig. 7

Cps2K
(SEQ. ID. NO. 52)

modify margins



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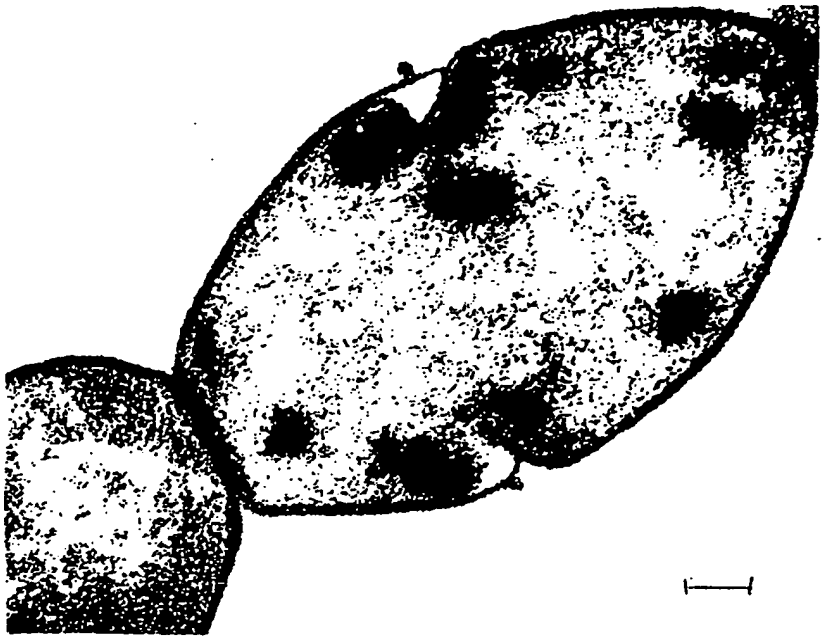

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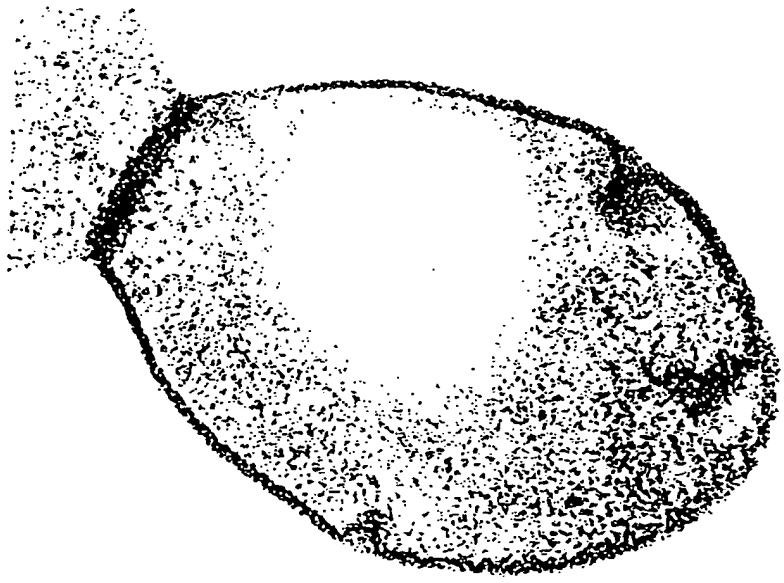

C

modify margins

better quality provided

Fig. 8

```
(1) 10508 AAGGGCACCT CTATAAACTC CCAAAATTGC GAATTTGGAG TTACGAAAGC CTTGTTAAAT CAA-CATTTA AATTTTAGAA AATTAGTTTT TAGAGCTCCC  10607  SEQ. ID. NO. 48
          |||||||||| || |||||||||| |||||||||| |||||||||| ||| |||| |||||||||| |||||||||| ||||| ||||
(2) 16985 GGGGGCACCT CTATAAATTC CCAAAATTGC GAATTTGGAG TTACGAAAGC CTTGTTAAAT CAA-CATCTTA AATTTTAGAA AATTAGTTTT TAGAGGTCCC  17084  SEQ. ID. NO. 49
          |||||||||| || |||||||||| |||||||||| |||||||||| ||| |||| |||||||||| |||||||||| ||||| ||||
(3) 19803 AAGGGCACCT CTATAAACTC CCAAAATTGC GAATTTGGAG TTACGAAAGC CTTGTTAAAT CAAACATTTA AATTTTAGAA AATTAGTTTT TAGAGGTCCC  19903  SEQ. ID. NO. 50
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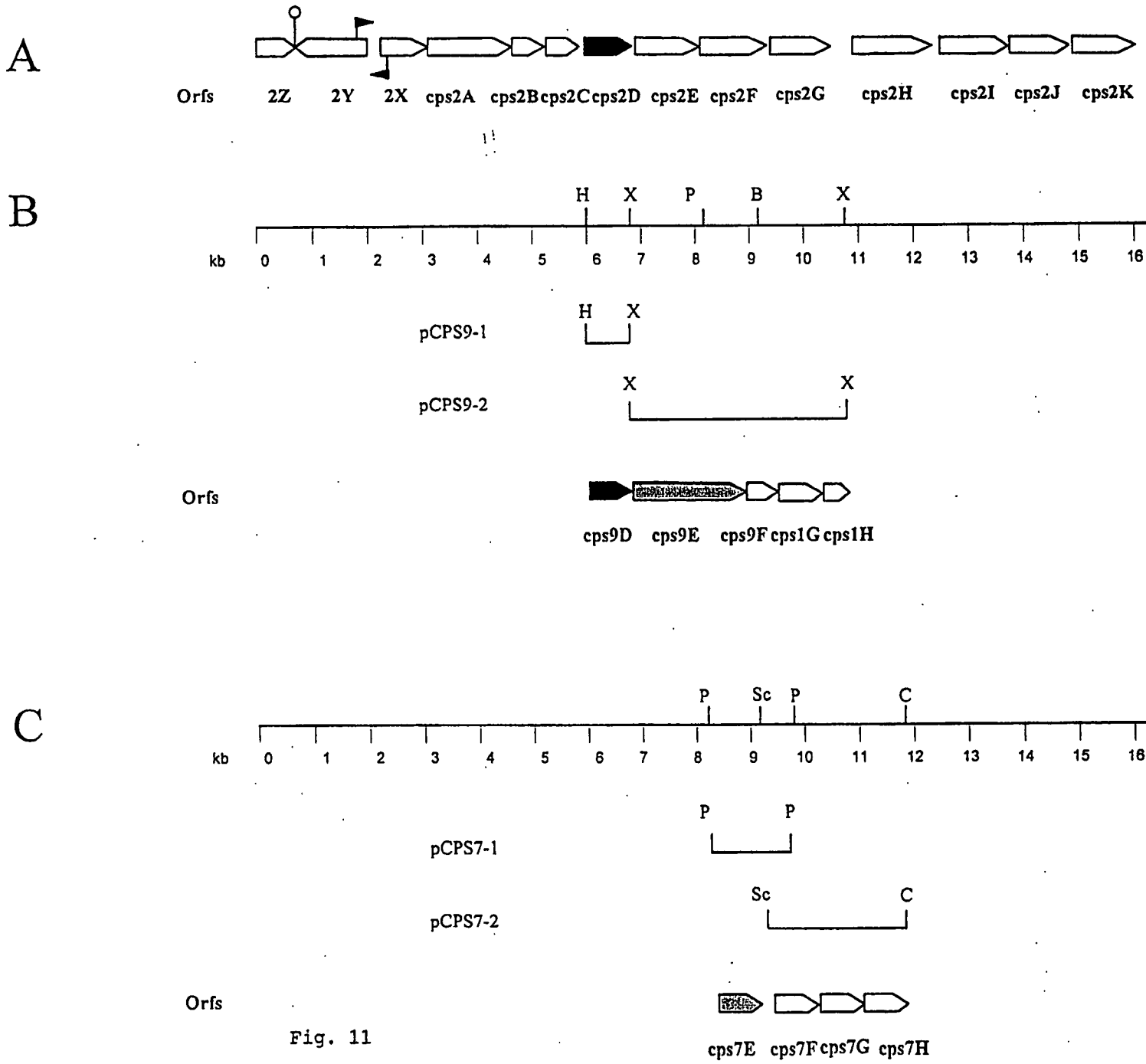
Fig. 10

modify margins


A
Orfs
2Z
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2X
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cps2E
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cps2G
cps2H
cps2I
cps2J
cps2K
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5
6
7
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9
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11
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13
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14
15
16
pCPS7-1
P
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Sc
C
Orfs
cps7E
cps7F
cps7G
cps7H

Fig. 11

better quality copy provided

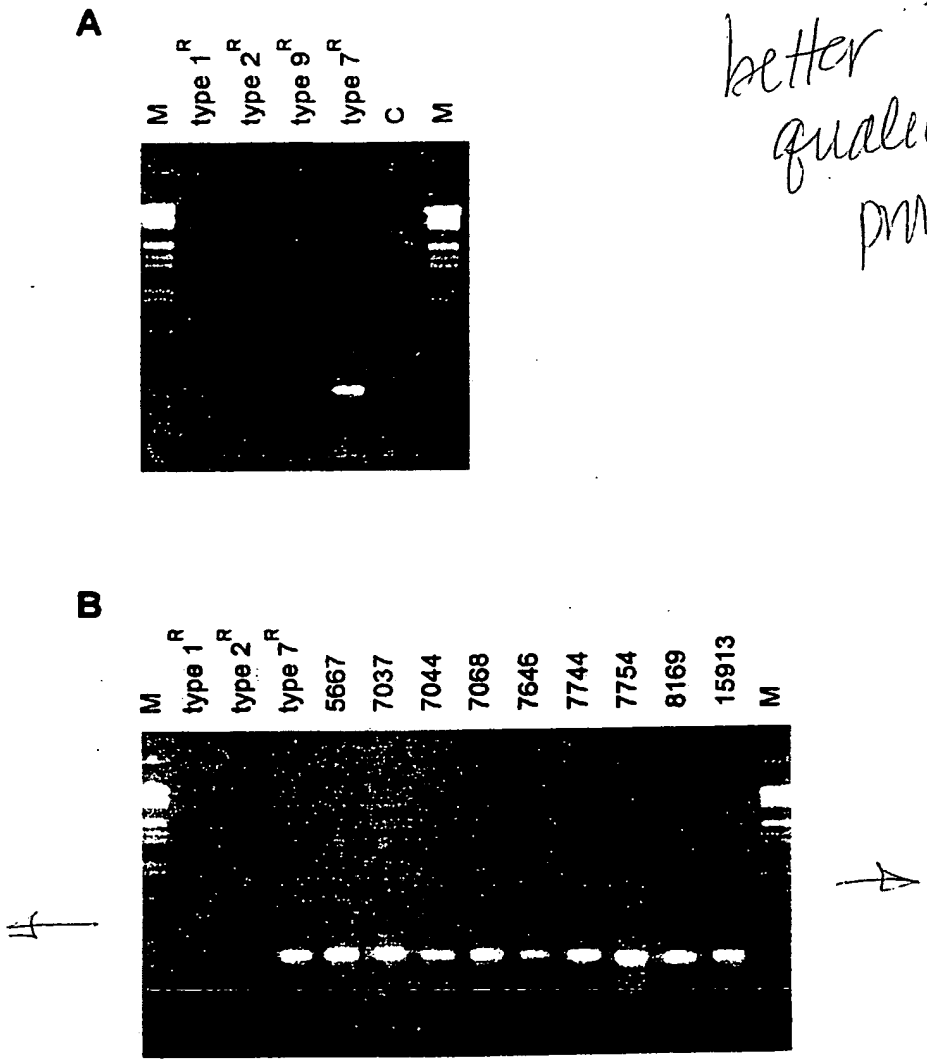

Fig. 12